THE EFFECTS OF AUTONOMIC DRUGS ON SWEAT SECRETION IN MAN*

by

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INTRODUCTION

SWEAT GLANDS.

The glandular structures of human skin have been classified according to the mechanism of secretion as holocrine or wholly secretory (the sebaceous glands), and merocrine or partly secretory (the sweat glands) (Ranvier,1887). Schiefferdecker (1922) further divided the merocrine glands into two sub-classes, the apocrine and the eccrine glands. The eccrine glands discharge a fluid secretion without loss of cellular constituents. In the apocrine glands the mechanism of secretion is more complicated, involving both a necrobiotic discharge and simple secretion. In mammals, with the exception of man, the apocrine glands are distributed widely over the body surface, while the eccrine glands are found only in certain restricted areas (e.g. the foot pad of the cat). In man, eccrine glands are present in large numbers in all areas, and it is the apocrine glands which are confined to particular regions, such as the axillae.

The eccrine glands are tubular glands. The diameter of the tube is almost uniform in its whole length, the secretory part forming a closed coil. The duct opens on the skin surface by a corkscrew-like channel which pierces the epidermis. The tubule (but not the duct) is overlaid with regular longitudinal

myoepithelium which probably helps to expel secretion from the gland (Richardson, 1949). The average number of glands per square cm. of skin is 100 - 300.

SWEAT is a clear, alkaline, hypotonic solution of plasma crystalloids. (Way & Mennesheimer, 1940). The sodium chloride content ranges from 100 - 600 mgm.%. In secreting a hypotonic fluid the glands are performing osmotic work: their capacity to do this is increased by adrenal mineralo-corticoids (Conn et al.,1946: Conn 1949) and diminished by fatigue (Ladell, 1945). Kuno (1950[a]) has recently pointed out that the sweat ducts have a rich capillary blood-supply which suggests that the cells have some function other than the mere passage of sweat. There is no evidence that they are concerned in secretion, but histochemical studies indicate that reabsorption may occur in the ducts. It is tempting to think that they may be responsible for the selective re-absorption of sodium and chloride from the sweat. A comparison of the sweat gland with the nephron of the aglomerular kidney would be an interesting study.

THE NERVE-SUPPLY TO THE SWEAT GLANDS. (Guttmann, 1931: List & Peet,1938[b]). The secretory activity of the sweat glands is under nervous control. From the anatomical point of view, the sweat fibres are sympathetic, leaving the spinal cord in the anterior roots D 1 - L 2 and relaying in the sympathetic ganglia. Post-ganglionic fibres to the trunk and limbs rejoin the spinal nerves

and are distributed with the cutaneous sensory nerves. (White,1930[b]: Woollard & Phillips,1932). Fibres to the head and neck, after relaying in the cervical ganglia (L.Guttmann,1940), run in the carotid plexuses to join the peripheral branches of the fifth cranial nerve distal to the sensory root (List & Peet,1938[d]). The existence of accessory sudomotor fibres of bulbar origin has been suggested by Wilson (1936).

Spinal sympathetic dermatomes were studied by Foerster (quoted by List & Pimenta, 1944) and proved to be much larger than the corresponding sensory dermatomes, preganglionic fibres from each root being distributed to four or five ganglia. L.Guttmann,(1938) found disturbances of sweat secretion in D 7 - 9 dermatomes in three patients with gall-bladder disease ("der Viszerosudorale Reflex"), and pointed out that there might be a dissociation between the area of sweat disturbances and Head's area of sensory disturbances. Reflex sweating of segmental distribution has also been described in angina pectoris (R.S. Palmer,1930).

The sympathetic fibres to the upper limb which are derived from segments D 2 - 6 or below, all pass through the second dorsal ganglion (Atlas, 1941: Smithwick,1942: Hyndman & Wolkin,1942[a]). This makes it possible to interrupt the sympathetic pathway to the hand without injuring the cervical sympathetic fibres which leave the cord in the first dorsal root and pass

upwards through the stellate ganglion. Removal of the second dorsal ganglion (Hyndman & Wolkin, 1942[a]) or division of the sympathetic chain below the third dorsal ganglion combined with section of either the white rami communicantes to the second and third ganglia (Telford, 1935) or the second and third spinal nerves (Smithwick, 1940[b]) abolishes all sweating in the upper limb. Since most of the cell stations are situated in the stellate ganglion these operations are essentially preganglionic interruptions of the pathway. The fibres to the lower limb have a longer course, leaving the cord at the level of D 10 - L 2 and relaying in the lumbar and sacral ganglia. Lower limb sympathectomy is also preganglionic, consisting in the removal of a section of the lumbar chain which usually includes the second, third and fourth lumbar ganglia. It has recently been shown (Boyd & Monro 1949) that in the lower dorsal and upper lumbar regions there are accessory sympathetic ganglia within the anterior primary rami. These ganglia are surgically inaccessible so that even after extensive thoraco-lumbar sympathectomies sweating may persist on the lower abdomen and thighs.

The mode of termination of autonomic nerve fibres has been studied by several techniques. Hillarp (1946) employed a methylene blue staining method to study the morphology of the pericellular apparatus. He found that the axons broke up into terminal ramifications which

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entered a "nervous ground plexus" within a network of anastomosing strands formed by a terminal Schwann plasmodium. This was directly superimposed on the effector cells, so that each cell was in contact with some part of it. The plexus was discontinuous suggesting that the system was organised into "neuro-secretory units" analagous to motor units. Several axons contributed to each unit. This conception was supported by experimental observations on partially denervated salivary glands (Hillarp, 1949 - see page 61). The pattern of the local sweat response to faradic stimulation which is due to a local nervous mechanism (Bickford 1938: Wilkins et al. 1938) also suggests that the terminal arborisations of the sweat fibres, though extensive, do not anastomose freely, the response usually covering an area of 5 - 15 sq,cm.

THERMAL SWEATING:

Experimentally, thermal sweating can be induced in three ways: by direct heating, by reflex heating and by raising the environmental temperature. Intense heat is needed to produce a direct response from the sweat glands and it is unlikely that this mechanism has any physiological significance: the critical surface temperature in Randall's (1947) experiments was between 39° and 45°C. By reflex heating is meant, for example, immersing both feet in hot water and studying the response in the upper limbs. After a latent period of 5 - 15 minutes vasodilation occurs in the hands and there is a rise in skin

temperature. Later generalised sweating appears. It has been shown that two factors are concerned in this response: the return of warmed blood to the hypothalamus and afferent nerve stimuli from the heated area (Ladell, 1945: Randall et al., 1948). There is evidence that the afferent nerve pathway is not the same as for the sensation of warmth (Issekütz et al.,1950). Cooling a limb inhibits thermal sweating by a reflex nervous mechanism. The critical level of environmental temperature for thermal sweating varies of course with the endogenous heat production. For normal subjects under basal conditions it is about 88°F. (31°C.)

Bazett (1950) described superficial (dermal) and deep (subcutaneous) temperature receptors, the latter being related to the deep venous plexus draining blood from the muscles. He suggested that the reflex response to external heating, in which the superficial receptors are stimulated, differs from that to internal heating (muscular exercise). In the first case the response is primarily vasodilator and sweating does not supervene until surface temperature exceeds 34°C: the second type of response utilizes sweating which is proportional to the existing surface temperature and maintains, rather than alters it.

The activity of individual sweat glands during sub-maximal thermal sweating has been studied by Kuno (1934, 1938) and by Randall (1946). It has been found that

* Footnote, page 7. A rise in skin temperature may also be a factor (Robinson et al.,1950).

the glands work in relays and are in addition subject to a general waxing and waning of activity which occurs simultaneously on various parts of the body surface and is obviously under the control of a centre, probably in the hypothalamus. As the environmental temperature is raised, more and more glands are called into action until a maximum is reached: further increase in the sweat response is achieved by raising the rate of secretion of individual glands. It has been calculated that individual glands can secrete up to 0.01 mgm. /min. (Randall & McClure, 1949). A total of three litres may be secreted in an hour during maximal sweating. Such a high rate of secretion cannot be maintained for long: even if water and salt are replaced by drinking, secretion begins to fall off after about an hour. The sweat electrolyte content rises as the glands fatigue, owing to their diminished capacity for osmotic work.* Another factor, to which Kuno (1950[b]) has drawn attention, is the increased gradient against which the cells have to operate owing to the high local concentration of NaCl in the extracellular fluid.

Evaporation is most efficient when the relative humidity of the environment is low and ventilation good. In a still, humid atmosphere little evaporation occurs and it has been suggested by Kuno (1934) that the inhibition of sweating which occurs in heat stroke may be an attempt to protect the body against a nett gain in

heat due to an intense activity of the sweat glands.

A good blood supply to the skin is needed for continued sweat secretion. If a tourniquet is applied to a sweating limb secretion falls off to very low levels after 10 - 30 minutes. An interesting observation arising out of this kind of experiment is that release of the tourniquet is followed by temporary inhibition of sweating on the opposite limb, due presumably to release of some humoral agent into the circulation from the ischaemic area. This agent probably acts centrally and not peripherally, since the inhibition of sweating on the opposite arm is not prevented by occluding the circulation to that arm immediately before release of the opposite cuff. (Randall et al. 1948). Patients with congestive heart failure have been found to sweat less than normal subjects in a subtropical climate (Burch, 1946).

The response to heating is modified by repeated exposure to high environmental temperatures over a period of 10 - 14 days. The process of acclimatisation to heat involves important cardiovascular adjustments as well as changes in the sweat mechanism itself. There is an increase in extra-cellular fluid volume and in cardiac output. On exposure to heat sweating is more profuse: it appears after a shorter latent period and at a lower rectal temperature. The sodium chloride content of the sweat is reduced by 60 - 70%. Conn (1949) has shown

that the fall in sweat NaCl is accompanied initially by a fall in urinary NaCl and by a negative nitrogen balance. Later the urinary electrolyte output returns to its original level, although the sweat NaCl remains low. These metabolic changes can be reproduced by giving pituitary adrenocorticotrophic hormone (ACTH).

Conn et al. (1946) had previously shown that the salt content of the sweat was reduced by desoxycorticosterone acetate (DOCA). The response of the sweat glands is not so prompt as that of the renal tubules: it is apparent about 18 hours after intramuscular injection. The two structures also differ in their capacity to maintain the response: whereas the urinary salt output "rebounds" after 2-3 days despite continued administration of DOCA, sweat NaCl remains at a low level as long as the hormone is given. When DOCA or ACTH is discontinued sweat NaCl rises far above the initial level, presumably owing to depression of endogenous hormone production. Conn and other workers also found that the sweat sodium was high in patients with Addison's disease and low in Cushing's syndrome.(1948)

The regional distribution of thermal sweating has been studied by several workers. Kuno (1934) gives the order of degree of sweating as 1) forehead, neck, some larger areas of anterior and posterior surface of trunk, lumbar region, dorsum of hand and adjacent part of forearm, 2) cheek, lateral surface of trunk and the greater

part of the extremities, 3) internal femoral regions and axillae, 4) palms and soles. These results have been confirmed by Burch & Sodemann (1943) and by Weiner (1945). It can be seen that the areas which sweat relatively little in response to thermal stimuli are those unfavourably situated for evaporation. Sweating on the palms and soles may actually diminish as a result of heating. Conversely, mental and emotional stimuli which elicit sweating on these areas may temporarily inhibit thermal sweating.

EMOTIONAL OR MENTAL SWEATING.

This form of sweating is most conspicuous on the palms of the hands but also affects the soles of the feet and, in some individuals, the axillae. It is elicited by a variety of mental and emotional stimuli, all more or less unpleasant, such as pain, fear, embarrassment and mental arithmetic. Extreme mental stress or violent sensory stimulation causes sweat to appear on the whole body surface. A similar general sweating can also be caused by minor sensory or emotional stimuli when the surrounding temperature is high.

Mental sweating appears suddenly and does not progress. When the stimulus is over it rapidly declines.

The psychogalvanic response was first described by Feré (1888). This response is the reduction in resistance of the skin to the passage of a low-voltage direct current

following various sensory stimuli. It is most easily recorded from the fingers and toes, but under favourable conditions can be obtained from all parts of the body surface. Carmichael and others (1948[a]) have shown that it has two components - sweat secretion and vaso-constriction. Changes in skin potential in response to psychological and other stimuli were reported by Tarchanoff (1890), and have been studied by Goadby & Goadby (1936, 1949). This e.m.f. response depends on unknown mechanisms, which do not include vasoconstriction (since exsanguination of a limb leaves the response temporarily unaffected). Like the resistance response it is abolished by sympathectomy. Potentials recorded from the cat's foot pad after induction shocks applied to the lumbar sympathetic are of very brief duration; "tetanisation" is not obtained until the frequency of stimulation approaches 150/min. (Richter & Whelan, 1943). It is claimed that the brief, monophasic nature of the response implies that it does not depend on the moisture liberated but rather on a change in permeability (?) of the sweat glands as they become activated.

Darrow (1937) has reviewed the neural mechanisms controlling palmar sweating. It can be elicited by stimulation of the premotor cortex. In man bilateral ablation of area 24 and part of area 32 may be followed by diminished sweating of the extremities (Pool, 1949).

CHEMICAL STIMULATION OF SWEAT GLANDS

The chemical transmitter at the sweat nerve-endings is acetylcholine (ACh). Dale & Feldberg (1934) showed that ACh appeared in the venous effluent of the perfused cat's foot when sweating was elicited by nerve stimulation. Sweating is inhibited by atropine.

Administration of parasympathomimetic drugs causes a secretion of sweat. The older observations were made with pilocarpine. There was a prolonged controversy about the exact site of action of this drug, some maintaining that it stimulated the gland cells directly, and others that it acted on the nerve-endings to cause a release of ACh. Langley (1922) showed that the response to intradermal injection of pilocarpine in the footpad of the cat was retained after nerve section and degeneration. He attributed the failure of other workers to get responses after denervation to the administration of the drug by remote subcutaneous injection and to the difficulty of detecting responses in adult cats with heavily keratinised pads. The direct action of pilocarpine on the sweat glands was also demonstrated by Hinsey & Cutting (1934) in the cat, and by Wilson (1934, 1936), Gurney & Bunnell (1942), and Palmer (1947) in human subjects.

In man subcutaneous injection of pilocarpine often causes nausea and urinary urgency in doses which produce

little or no generalised sweating. Acetylcholine itself has of course no general effects when given subcutaneously owing to its rapid destruction by the true cholinesterase present in the blood and tissues. Acetyl-beta-methylcholine (mecholyl)* is more stable; but, like pilocarpine, it causes undesirable side effects. Carbaminoyl-choline (carbachol) has a specially powerful action on the bowel and bladder. Furfur-trimethylammonium iodide (furmethide) is a parasympathomimetic substance described by Myerson et al. (1940) and Fellows & Livingstone (1940). According to S.A. Guttmann (1944) it can be relied on to produce generalised sweating without unpleasant side effects when injected subcutaneously in a dose of 5 mgm.

Local stimulation of sweat glands by parasympathomimetic agents introduced into the skin by intradermal injection or iontophoresis is discussed in the following section. Koppanyi (1945) has recently advocated the use of a weakly muscarinic diene alcohol (hexadienol) which is effective when applied to the skin surface.

* Now known as Methacholine.

The <u>original aim</u> of the present work was to find out how far overactivity of autonomically innervated organs was due to:

(1) overaction of nervous control

(2) excessive sensitivity to the chemical transmitter.

The sweat glands were chosen owing to their accessibility for observation and for injection and the relative simplicity of their response to drugs. They have the further advantage of being easily isolated from their nerve supply by procaine nerve block.

CHAPTER 1.

METHODS

MEASUREMENT OF SWEAT RESPONSES.

A number of methods have been described for the measurement of sweat gland activity.

Weighing. The whole body can be repeatedly weighed on a Sauter balance (which has an accuracy of 0.1 Gm.). The difference in weight less the water content of the expired air less the amount by which the weight of CO_2 eliminated exceeds the weight of oxygen absorbed represent the total water loss from the skin. (At low environmental temperatures this comprises the sweat secreted by palmar and plantar glands (less than 5%) and the insensible water loss through the rest of the skin. (d'Alton et al., 1948).

Sweat collections. Regional differences in the rate of sweating have been studied by Kuno (1934) and by Weiner (1945) whose method was to collect sweat in shallow brass cups and to determine the weight gain of absorbent swabs with which the cups were mopped out. The mean output of individual sweat glands has been measured by Randall & McClure (1949) by means of simultaneous sweat collections and iodine-starch paper tests (see below). This proved to be of the order of 10 microgrammes/min.

during maximal stimulation. A really elegant technique was described by Neumann, Cohn and Burch (1941), in which sweat is picked up from a chamber applied to the skin by a current of dry oxygen, and recondensed in a series of cooled aluminium coils which were weighed at the beginning and end of the observation. An illustration of this apparatus appears in the paper by Burch & Sodeman (1943).

There are numerous colorimetric methods for the detection of sweating and some of these have been adapted to yield semi-quantitative results. The original method was that described by Minor in 1927 in which a starch-iodine mixture is painted on the skin and turns blue in the presence of sweating. Later L. Guttmann introduced Quinalizarin powder which changes on wetting from grey to an intense purple. These methods lend themselves to photographic recording and provide beautiful illustrations to the series of papers by List & Peet (1938-9) and to Guttmann's (1931) review. We have made use of a modification of Minor's (1927) method described by Randall (1946) in which the skin is painted with 3% iodine in 95% alcohol and a piece of starch paper is applied to the test area for ½ minute. Each active sweat gland shows as a tiny, dark blue point on the paper. The number of dots is counted with a lens: their size gives an impression of the rate of secretion

from individual glands. The iodine must be renewed frequently, otherwise the dots become very faint. To avoid smudging it is best to hold the paper on the skin with forceps. Similar prints can be made with tincture of ferric chloride and tannic acid paper (Silverman & Powell, 1944), and with untreated paper applied to the skin, floated in silver nitrate solution and "developed" in ultra-violet light. (Gurney & Bunnell, 1942). We even found it possible to visualise sweating by painting the skin with 10% starch and sodium hypochlorite and incorporating 5% sodium iodide in the test injection. We hoped to measure the latent period in this way but the colour reaction developed too slowly.

The measurement of skin electrical resistance was introduced in Charcot's clinic many years ago (Vigouroux, 1879). Minor (1927) recommended it as a substitute for the colorimetric method in negroes. Richter & Levine (1929, 1937) have established that the skin resistance depends on the activity of the sweat glands and is greatly increased by their denervation in both monkeys and human subjects. Reference has already been made to the proof by Carmichael et al. (1940[a]) that reflex vasoconstriction as well as sweating causes a fall of the skin resistance. In the conditions of our experiments a fall of skin resistance has always indicated sweating except where the skin has been

injured or where a powerful vasoconstrictor has been injected. Alternate electrical and iodine-starch paper readings agree very well on the whole (Table 6), except that a) an aggregation of secreting glands round the point of puncture may be missed by the exploring electrode so that the current recorded is proportionately too small or b) a small number of actively secreting glands may wet the skin enough to give quite a large fall in resistance. The two readings diverge seriously only in the adrenaline experiments (Table 6) for reasons discussed above. Taken together they constitute a very reliable technique for detecting sweating. The particular virtue of the electrical method is that readings can be taken quickly from a number of control areas as well as from the injection site so that the reflex sweating which occasionally follows the needle-prick can be easily distinguished from a direct action of ACh on the sweat glands. This reflex sweating may be generalised or localised. In the first case it is due to a central reflex and is strictly comparable to the psychogalvanic response on the fingers: in the second case it extends over an area of 5 - 15 sq.cm. and resembles the sweat response to faradic stimulation described by Bickford (1938) and Wilkins et al. (1938) and attributed by them to an axon reflex. The time course of these reflex responses is quite different from

that of the response to chemical stimulation, the reflex sweating appearing almost instantaneously and quite quickly dying away, while the direct response has an appreciable latency, continues to increase for a minute or two, and lasts 10 - 20 mins. or longer. Any well-marked response which quickly decays (or any response which is 'out of series') is an indication for repeating the injection. There is one chemical substance which appears to cause responses of the axon reflex type, namely nicotine - this will be dealt with in a later section.

The apparatus used for electrical measurements is extremely simple. It consists of a 9 V. battery connected to two electrodes through a variable resistance. The current flow is registered by a galvanometer reading 0-24 micro-amps. in 0.2 micro-amps. divisions. The electrodes are a saline pad incorporating a chlorided silver wire, which is strapped to the upper arm, and a silvered brass disc of 15 mm. diameter, with a non-conducting handle, which is applied lightly to test and control areas. Needle punctures must be carefully avoided as there is a risk of damaging the galvanometer owing to the very low resistance at the puncture site. If the exploring electrode is too small it tends to leave an impression on the skin so that after repeated applications a fall of skin resistance due to trauma

occurs. This circuit does not, of course, measure skin resistance directly: for that a more elaborate circuit is required (Smithwick, 1940[a]). But since we are concerned only with changes in resistance or differences between one area of skin and another, it is enough to record the amount of current flowing through the test area when control readings on non-sweating areas are 0 - 0.2 micro-amps. (Haxton, 1947: Barcroft & Hamilton, 1948[a b]). The resistance of the tissues other than the skin is relatively small, so that it is immaterial to which arm the indifferent electrode is attached.

Application of Drugs to the Sweat Glands

Intravenous infusion. - Since it was important to study the sensitivity of the sweat glands on the palm of the hand, where intradermal injections are apt to be painful, a few preliminary experiments were done in which mecholyl and acetylcholine were given intravenously. The drugs were given by slow infusion with a constant speed infusion apparatus. Weiss & Ellis (1934) reported that 20 mgm/min. of ACh constantly produced minimal effects and that the corresponding dose of mecholyl was 0.1 mgm/min. Carmichael & Fraser (1933) emphasised the pronounced variability of the response to ACh. We found (in six subjects) that with mecholyl at rates below 0.1 mgm/min. the only effect was flushing of the

face and local flushing and sweating over the vein. At a rate of 0.125 mgm/min. there was in addition increased salivation, slight tachycardia and tightness in the chest. At 0.15 mgm/min. sweating appeared but was confined to the forehead and cheeks. In one subject the rate was increased to 0.3 mgm/min. without producing increased sweating of the hands. Acetylcholine was given to two subjects. No effect was observed with rates of infusion up to 32 mgm/min. 50 mgm/min. produced flushing of the face and a slight feeling of constriction in the chest. With 75 mgm/min. there was a marked feeling of warmth and flushing, tachycardia, and a sense of constriction in the chest. Sweating broke out on the forehead, nose and upper lip but there was no increased sweating of the palms or forearms.

Intradermal injection. - It was clear from these results that intravenous infusions were unsuitable for testing the sensitivity of the sweat glands. We therefore turned to local injection of parasympathomimetic drugs. To minimise trauma special short-level intradermal needles were used (Hawkins $4\frac{1}{2}$/10mm. x $\frac{1}{2}$ inch) and only a minute volume of solution was injected. This was usually 0.01 cc. measured by an "Agla" micrometer syringe. The needle was pushed along in the skin for about 1 cm. before making the injection, so that it would be possible to avoid the point of puncture in taking

electrical readings. After withdrawing the needle the area was carefully dried. We aimed at making a deep intradermal injection so as to get as near the sweat glands as possible. When we came to check this point by Indian ink injections in the cadaver it was found that some of the injections were actually subcutaneous, although most of them were shown histologically to be well placed in relation to the glands. In the case of acetylcholine depth of injection does not seem to be very important (Table 1) provided a) it is not so superficial as to traumatise the epidermis and b) not so deep as to be actually below the deep fascia.

Sites of injection. - The flexor surface of the forearm well above the wrist was the site most often used for injections. In a cool environment (R.T.=18-20°C) this area does not sweat spontaneously and so provides a good background against which responses can be studied. After eliminating pain sensation and spontaneous sweating by blocking afferent sensory and secretomotor impulses in the median nerve with procaine, it was also possible to study responses on the palm of the hand. In Table 2 responses to 0.01 cc. of mecholyl 10^{-3} injected at two sites on each forearm are compared. It can be seen that the response is greater in this case on the right side than on the left; there is a smaller difference between the second pair of sites and the first. Table 3

shows the variation between one forearm and the other in six subjects tested with acetylcholine. On the whole the differences are small, the smallest effective concentration lying within a tenfold range on the two sides. Rather larger differences appeared when palm and forearm sensitivities were compared (Table 4), the palmar glands tending to respond to smaller concentrations than those on the forearm. Krause (quoted by Kuno, 1934) found 2736 glands per square zoll (? 11 sq.cm.) on the palm compared with 1123 on the flexor surface of the forearm. Now it is obvious from the study of starch paper prints that individual sweat glands vary in their sensitivity to acetylcholine. If the numbers of glands sensitive to different concentrations of ACh are distributed in the same way, one would expect to find more glands capable of responding to very low concentrations of ACh on the palm than on the forearm.

Preparation of solutions. - The results of injecting slightly different concentrations of ACh (see Table 3, subject J.A.F.) were rather inconsistent. Because of this, and because of the variations in sensitivity between the two sides and between different sites on the same forearm, it was clearly impossible to work to the same degree of accuracy as if one were studying isolated tissues. Since differences of less than tenfold in the smallest effective concentration of ACh were unlikely to

be significant we decided to make up serial tenfold dilutions and to omit the testing of intermediate concentrations. The conventional notation of 10^{-3}(=1:1000), 10^{-4}(=1:10,000), 10^{-6}(=1:1,000,000) etc. has been used.

Crystalline acetylcholine hydrochloride (Roche) was used. The need to prepare sterile solutions for injection introduces certain difficulties. Owing to its instability Acetylcholine has to be made up freshly for each experiment. It is inconvenient to sterilise pipettes and flasks frequently for this purpose. Dilutions made with sterile syringes and stored in test tubes are reasonably accurate provided precautions are taken against the adsorbing effect of the glass. We suspected that our dilutions were unreliable at a very early stage, when we were getting responses to fantastically low concentrations of ACh. Although the reservoir of saline was changed frequently, the same syringe was being used to dilute from 10^{-1} to 10^{-15}. When solutions prepared in this way were compared on the frog rectus by Dr.F.Hobbiger with solutions prepared with a series of pipettes and flasks, it was found that the syringe solutions deviated progressively from the expected line below 10^{-5} and that below 10^{-7} scarcely any further dilution occurred (Fig. 1.). Presumably ACh ions are adsorbed by the glass from concentrated solutions and come off again into dilute solutions. No amount of

washing out will get rid of this source of error. One must either treat the glass ware with a non-adsorbent substance such as silicone or else use a series of syringes in preparing solutions. The concentration of ACh in a solution prepared by the multiple-syringe method and purporting to contain 10^{-7} was found to be 1.2×10^{-7} by comparison with a solution prepared by the pipette-and-flask technique. The solutions were compared on the frog rectus preparation by Dr.Hobbiger. A similar comparison on human sweat glands also gave satisfactory results. (Table 5). It was thus clear that the multiple-syringe technique was sufficiently accurate for our purposes, and we have used it throughout the whole of the work to be described. Similar precautions were observed with the syringes and needles used for giving the injections. Where a syringe was used more than once it had previously contained a weaker, and not a stronger solution of the same drug.

The diluent used was sterile normal saline with a pH of 5.5 - 6.0 (glass electrode). This produces no response when injected into the skin.

In one or two experiments drugs were introduced into the skin by iontophoresis (Wayne, 1933). This method of course gives qualitative results only, but it is particularly useful for atropinising an area of skin where injection would be painful. Carmichael et al.

(1940[a]) for example, used it to demonstrate that the psychogalvanic response could still be obtained from the finger-tip after all sweat-gland activity had been suppressed by atropine, proving that the response had a vasomotor component. The method was also very ingeniously used by Barcroft and co-workers (1943), in their plethysmographic studies of muscle blood flow, to blanch the skin of the entire forearm with adrenaline. Most autonomic drugs can be introduced into the skin in this way, and there are papers describing iontophoresis of pilocarpine and adrenaline (Giraudeau, 1931 and Ackermann, 1936, 1938), mecholyl (Martin, 1937) and dibenamine (Last et al., 1949). We have been able to produce local sweating by iontophoresis of acetylcholine and carbachol as well as mecholyl. A current density of 1 mA/sq.cm. for about 10 mins. was suitable, the anode being the same brass electrode used for skin resistance measurements with a pad of filter paper soaked in a 10^{-3} or 10^{-4} solution of the drug applied between it and the skin.

SUMMARY

Methods of measuring sweat responses are reviewed. In the present work both the iodine-starch paper test and the skin electrical resistance test have been employed.

Intravenous infusions of acetylcholine (ACh) and mecholyl were found to be unsuitable for testing the sensitivity of the sweat glands because of unpleasant side effects.

The technique used for intradermal injections is described. Injections were made into the flexor surface of the forearm and, after procaine block of the median nerve, into the palm of the hand. Variations in response between different sites of injection have been recorded.

The preparation of dilute solutions of ACh requires special precautions to avoid the effects of adsorption of ACh on to glassware.

Examples are given of the value of iontophoresis.

CHAPTER 11.

THE RESPONSE TO ACETYLCHOLINE.

The injection of a small volume of acetylcholine or mecholyl solution into the skin constantly produced a sweat response which was roughly proportional to the concentration injected. The response was inhibited by intravenous and local atropine (Tables 7 and 8), and potentiated by anticholinesterases (Table 9). Using progressively weaker solutions it was possible to determine a threshold concentration below which no response was elicited.

Nicotine-like effects.

It has been claimed (Coon & Rothman, 1941) that locally injected ACh stimulates the sweat glands by two mechanisms: a) A direct muscarine-like action on the cell receptors: b) a nicotine-like action on the nerve endings producing an axon reflex. The efferent side of the axon reflex of course involves transmission by ACh so that both types of response would be abolished by atropine. The evidence accumulated by Rothman and his co-workers very strongly suggests that reflex sweating to ACh can occur, but we have never been convinced that sweating occurred in our subjects beyond the probable area of diffusion of ACh. On the other hand, we have occasionally seen reflex pilomotor stimulation with 10^{-2} to

10^{-4} ACh, another axon reflex described by these workers, (Coon & Rothman, 1940). We have also confirmed that nicotine can stimulate sweating by this mechanism, (Table 14). The response in subject J.H. was obtained in spite of blocking the cutaneous nerve with procaine and extended over an area 2-3 cm. in diameter. It appeared abruptly and quickly decayed. The blocking effect of Tetraethylammonium (TEA), which was noted by Janowitz & Grossman (1949) but denied by Issekutz et al. (1950), is easily demonstrated provided the TEA is injected some minutes before the nicotine (Table 14). A response was elicited 20 days after upper dorsal sympathectomy (Telford operation) in one subject. This confirms the view advanced on anatomical grounds (p.4) that the section is preganglionic. These effects of nicotine and ACh on sympathetic terminals are comparable with the centripetal discharges set up in sensory afferents by close intra-arterial injection of nicotine-like substances (Brown & Gray, 1948).

Comparison of ACh and mecholyl thresholds (Table 10) gave a rough idea of their relative potency. The mean mecholyl threshold in this small series was 10^{-6}, the mean ACh threshold being somewhat under 10^{-4}. Mecholyl is therefore about 200 - 400 times more potent than ACh by intradermal injection. This agrees well with the relative potency of the two drugs given by intravenous

infusion, 0.125 mgm/min. of mecholyl and 50 mgm/min. of ACh producing comparable effects. The maximum potentiation of ACh by anticholinesterases was of the order of a hundredfold or less, so it seems likely that the high relative potency of the beta-methyl ester is due to something more than its resistance to enzymatic hydrolysis. It would be interesting to compare the two drugs in skin areas previously treated with an anticholinesterase.

The time course of the response to mecholyl and ACh was rather different as one would expect, the mecholyl response decaying much more slowly (Fig. 2). With both drugs there was a latent period of 10 - 30 seconds before the response appeared.

Variations in Response.

With the object of imitating the release of the natural chemical transmitter as closely as possible, acetylcholine itself was used in most of the experiments to be described. The smallest effective concentration was determined in 50 normal young adults (25 of each sex). In 47 subjects the ACh threshold was between 10^{-3} and 10^{-6}: one responded on repeated occasions to 10^{-7} and one required 10^{-2} to produce a response. Only one failed to respond to 10^{-2} ACh. (Table 11). There was no significant sex difference, in contrast to the findings of Gibson & Shelley (1948) who studied the iodine starch paper count

after injecting fixed concentrations of ACh and pilocarpine and reported that the sweat glands in females were much less responsive than in males. Kahn & Rothman (1942), using Minor's method to visualise sweating, reported negative to slight responses to 10^{-3} ACh in 90% of 41 women compared with moderate to very strong responses in 95% of 59 men. The differences may have been due to a diffusion effect since we were able to spread the response to a given concentration of ACh over a wider area of skin with hyaluronidase, although we could not usually lower the ACh threshold (Table 12). On the other hand, Janowitz & Grossman (1950) studied a small group of males and females and found that the ACh threshold was about 10^{-3} in the women compared with 10^{-5} in the men. Since only five subjects of each sex were tested little significance can be attached to this result.

Myerson, Loman & Rinkel (1937) gave mecholyl to a number of schizophrenics and noted that some patients in whom 10^{-3} was enough to produce visible sweating in summer required 5×10^{-3} for a "good response" in November. We also noted a tendency for the ACh threshold to fall in summer (Table 13), Subject G.M.'s threshold was followed repeatedly over a twelve month period and fell from 10^{-3} in January to 10^{-5} in July and August, returning to 10^{-3} in November. (All observations were

made at approximately the same room temperature). I hoped to be able to show that the increased sensitivity of the glands is associated with acclimatisation to heat, but have not yet had an opportunity to study subjects under suitable conditions. Conn (1949) showed that the process of acclimatisation involves increased secretion of pituitary adrenocorticotrophic hormone. There is indirect evidence that this is not the humoral agent concerned in the seasonal variations in ACh threshold since one of our patients with hypopituitarism and another with Addison's disease responded to low concentrations of ACh.

With the exception of one woman aged 31 with congenital anhidrosis in whom complete lack of response to ACh was associated with absence of sweat glands on biopsy, there was no correlation between sweat function and sensitivity to ACh. Some subjects who sweated normally in hot weather were relatively unresponsive to injections and others with marked hypohidrosis proved to be quite sensitive. Patients with hypopituitarism and hypothyroidism had thresholds as low as 10^{-6} ACh. Comparison of hyperhidrotic subjects with a control group revealed no difference in the range of ACh threshold. (See page 69).

Differences in ACh threshold are not due to variations in the cholinesterase content of the skin. The

maximum potentiation of the ACh response by anti-cholinesterases was of the order of a hundredfold. The ACh threshold, on the other hand, varied over a range of more than a hundred-thousandfold. Moreover, potentiation was obtained in sensitive as well as insensitive subjects.

Until more is known about the factors which delay the onset of the response to injected ACh (pp.38-42), the significance of variations in sensitivity cannot be assessed.

Potassium.

The release of ACh at peripheral cholinergic nerve endings by intra-arterial injection of potassium chloride was demonstrated in the cat by Feldberg & Guimarāis (1936). It was suggested by Brown & Feldberg (1936) that the nerve impulse was accompanied by a wave of propagated potassium ions which liberated ACh at the nerve terminals. A solution of Ringer-locke plus 1.2% KCl as described by Brown & Gray (1948) was diluted to a final concentration of 10^{-3}. Injected into the skin this caused no sweating. The injection was repeated with higher concentrations up to 10^{-2} which caused a mild stinging sensation without producing a sweat response.

Effect of Nerve Block and Nerve Section on the ACh Response.

The effects of procaine nerve block, preganglionic

sympathectomy and peripheral nerve section on the ACh threshold have been examined. Owing to the variable anatomical course of the cutaneous nerves to the forearm it is helpful to locate them with a weak faradic stimulus as described by Trotter & Davies (1909). The stimulus is applied to a series of points in a line across the flexor surface of the forearm about an inch below the elbow, the course of the nerves being revealed by a characteristic fluttering sensation in the extreme peripheral part of the area which will be rendered anaesthetic. Usually a medial and lateral branch are found at this level; sometimes a central branch is also present. 1-2 cc. of a 4% solution of procaine containing 1:200,000 adrenaline was injected subcutaneously near each nerve. In most cases at least one branch was successfully blocked in this way, as shown by anaesthesia and absence of reflex thermal sweating. The threshold concentration of mecholyl or ACh was determined simultaneously in the anaesthetic area and on the opposite forearm in six subjects. (Table 15). In no case was there any significant difference.

Repeated observations on a small series of cases subjected to upper dorsal sympathectomy (preganglionic) showed that there was no great change in the excitability of the sweat glands by injected ACh (Table 16). Not all the limbs were followed over a period but eight examined

6-12 months after operation, and showing a minimal or absent response to reflex heating, sweated after intradermal ACh in concentrations down to 10^{-6}.

The effect of complete denervation was studied in a man who had suffered a lacerated wound of the left supra-trochlear region twelve months previously, the ulnar nerve being severed in two places. Cutaneous sensibility and reflex sweating were absent in the distribution of the ulnar nerve in the forearm. The sweat glands in this area did not respomd to ACh in concentrations up to 1%. On the corresponding part of the opposite forearm, after procaine nerve block, there was a good response to 10^{-4} ACh. (Starch paper 20 ; 6.0 micro-amps.) and a profuse response to 10^{-2} (Starch paper - over 100 : 18.0 micro-amps.).

It was reported by various workers, quoted by Langley (1922), that the sweat response to remote subcutaneous injection of pilocarpine in cats disappeared after denervation of the foot. On the other hand local local injection of 1% pilocarpine into the foot pad still caused sweating 42 days after section of the sciatic and popliteal nerves (Langley & Anderson, 1904). A response was also obtained in 4/6 animals 12-38 days after cutting the sciatic or posterior tibial nerves (Langley 1922). Hinsey & Cutting (1934) investigated the response to injection of pilocarpine into the foot pad after

lumbar sympathectomy and found that it was unimpaired for periods up to several years.

The advantages of local rather than remote subcutaneous or intravenous injection of test drugs have already been pointed out, and the reports from a number of sources (List & Peet, 1938[c], Schörcher 1939, L. Guttmann 1940, Palmer 1947), that in human subjects the sweat glands become more or less refractory to remote subcutaneous injection of pilocarpine or mecholyl after sympathectomy will not be further discussed. Three papers have appeared on the response to intradermal injection of mecholyl and ACh after sympathectomy: 1) Gurney & Bunnell (1942) reported that sweating still occurred after intradermal injection of 2.5×10^{-6} mecholyl in two subjects tested 10 days and one year after preganglionic sympathectomy. Skin biopsy showed no change in the appearance of the sweat glands compared with normal areas. 2) Kahn & Rothman (1942) investigated 10 subjects after post-ganglionic sympathectomy and found a diminished or absent response to ACh and mecholyl as early as $3\frac{1}{2}$ hours after operation, becoming consistently negative after a period of fluctuation lasting 2-62 days. They reported similar results in cats. They found no morphological changes in the denervated glands on biopsy, confirming Adson, Craig & Brown (1935). 3) Janowitz & Grossman (1950) studied

9 subjects after post-ganglionic sympathectomy. In 4 subjects the response to ACh (1:10 to 1:1000) disappeared 30, 38, 48 hrs., and 7 days after operation. The other 5 were tested between 3 days and 7 months after operation and showed no response. In 10 other subjects the local sweat response to hexadienol was lost after post-ganglionic sympathectomy. No phase of sensitisation to ACh was seen (Cannon, 1939).

It is thus clear that neither procaine nerve block nor preganglionic nerve section affects the sensitivity of the sweat glands to ACh. The response does disappear after procedures which destroy the peripheral autonomic fibres. This is not to say that ACh stimulates the glands through the nerve endings, since the disappearance of the response does not always coincide with the degeneration of the peripheral fibres but may be delayed for as long as two months after nerve section. The glands do not become atrophic, and retain their power of secretion in response to direct thermal stimulation (Saito, quoted by Kuno, 1934: Janowitz & Grossman, 1950). It is possible that denervation initiates a molecular rearrangement on the cell surface leading to disappearance of "specific receptor areas" as defined by Clark, (1933). This may be a reversal of the process by which sensitivity is acquired in embryo, since Armstrong (1935) has shown that the response of the Fundulus heart to ACh does not

appear until after the cells have received their innervation.

Latency of the ACh Response.

This was measured rather crudely by holding the exploring electrode over the site of injection and timing the interval between the injection and the first movement of the galvanometer. After intradermal injection of a weak solution of ACh in the forearm there was a latent period of 30 - 60 seconds before sweating was detectable. This delay could be reduced to 10 seconds by increasing the concentration of ACh injected, which suggested that it was mainly due to diffusion of ACh between the site of injection and the sweat gland receptors. Very high concentrations of ACh (up to 10^{-2}) were then tried, and a larger volume of solution was injected (0.1 cc. instead of 0.01 cc.). To our surprise the latent period was not further reduced. Several different subjects were tested but none was found in whom secretion was detectable within 10 seconds after injection.

In contrast with this finding, nerve stimulation produced a fall of plantar skin resistance within 1 - 2 seconds. (This result was obtained by electrical stimulation of the peripheral cut end of the lumbar sympathetic at operation in a human subject). Moreover, it was repeatedly noted that reflex sweating elicited by

a painful needle-prick appeared "almost instantaneously". Accurate measurement of the latency of the psychogalvanic response has shown it to be of the order of 2 sec. (Carmichael et al., 1940[a]). The delay at the neuro-effector junction is 100 - 200 milli-seconds (Brown,1937).

Further experiments were done in chloralosed cats with the assistance of Dr. F. Hobbiger. A similar difference in the latent period following nerve stimulation and local injection of ACh into the foot pad was found. Close intra-arterial injection of ACh (0.3 cc. of a 10^{-2} solution into the anterior tibial artery) caused "almost immediate" muscular contractions, but sweating could not be detected until 8 - 10 seconds after injection.

In an attempt to account for these observations a number of factors were considered:-

a) The secretory portion of the sweat gland is surrounded by myoepithelium which probably helps to expel secretion. We are ignorant of the coordination and control of this myoepithelium (Richardson, 1949). During nerve stimulation contraction may perhaps be elicited by some mechanism other than the release of acetylcholine at the nerve-ending. After intradermal injection of a mixture of adrenaline and acetylcholine the latent period was found to be as long as after ACh alone. Similar results were obtained with mixtures of (1) histamine and ACh and

(2) potassium chloride and ACh. The myoepithelium of the mammary gland responds to posterior pituitary extracts (Turner & Cooper, 1941: Folley, 1947). Mixtures of oxytocin and vasopressin with ACh were therefore tested: there was no appreciable shortening of the latent period. From these negative results it is concluded that none of the substances mentioned is likely to be concerned in the transmission of nerve impulses to the myoepithelium of the sweat tubules. The possibility has not been excluded that the relatively prompt appearance of secretion after nerve stimulation is due to contraction of the myoepithelium.

b) Injected ACh might have to cross some "barrier" in order to reach the site of liberation of transmitter. This might consist of a "cholinesterase filter" surrounding the neuro-effector junction. Prior injection of TEPP did not reduce the latent period. A similar latency was noted with carbachol which is not affected by cholinesterase, as well as with mecholyl and pilocarpine.

c) The barrier might be the cell membrane itself, if the nerve endings were actually intraprotoplasmic. Various methods of increasing permeability were tried, including ischaemia by local pressure or tourniquet, prior injection of procaine or histamine and addition of hyaluronidase to the injected ACh solution. None of

these measures reduced the latent period below 10 sec. There is both histological and pharmacological evidence against the suggestion that the release of transmitter is intracellular. Hillarp (1946) describes the autonomic nerve-endings as "a nervous ground plexus directly superimposed on the effector cells and interwoven between them", and denies the existence of intraprotoplasmic nerve endings. Cook (1926) showed that on the frog heart methylene blue had an atropine-like action when applied to the cell surface which disappeared when the dye had penetrated within the cells. Intracellular administration.of ACh in striated muscle does not elicit contraction (Gerard, 1946). Various drugs (Narcotics, HCN, H_2S) injected into amoebae do not produce the characteristic actions which are readily elicited by application to the external surface (Hiller, 1927: Brinley, 1928[a,b]). Clark (1933) has pointed out that the minimal effective dose of ACh for inhibition of the frog heart, if spread out in a monomolecular layer, would occupy only 1/6000 of the cell surface. He interpreted this in favour of the concept of specialised receptor areas on the cell membrane and not as evidence for an intra-cellular site of action.

d) Acetylcholine might be temporarily fixed at the site of injection by some physico-chemical process, such as adsorption or combination of the solvent with the hydro-

-philic ground substance described by Day (1948). This substance lies between the main fibrous components of loose connective tissue and combines with injected water to form an oedematous node (Ranvier's Boule d'oedème). It is not clear whether or not the hydrophilic property is due to hyaluronic acid: in any case, hyaluronidase does not abolish the latent period.

e) Injected material might pass into the skin lymphatics (Hudack & McMaster 1933: McMaster 1942). When injected dyes are studied with a dissecting microscope very little of the material is found in the interstitial tissue, except after trauma or inflammation. Most of it invariably passes into the skin lymphatics. It is unlikely that this would delay the arrival of such a highly diffusible substance as ACh at the cell membrane by ten seconds. Moreover, local trauma, histamine etc. did not abolish the latent period. The delay after intradermal and intra-arterial injection was of the same order.

Thus no entirely satisfactory explanation can be offered for the long latent period of the sweat response to intradermal ACh. Taken together with the lack of correlation between sensitivity to intradermal ACh and spontaneous tendency to sweat, it calls for caution in the interpretation of chemical tests of sweat gland excitability.

SUMMARY:

The sweat response to intradermal ACh was inhibited by atropine and potentiated by anticholinesterases.

Axon reflex responses to ACh and nicotine are discussed.

Mecholyl was 200 - 400 times more potent than ACh.

The smallest effective concentration of ACh (ACh threshold) in 50 normal subjects varied from 10^{-7} to 10^{-2}. No significant sex difference was found. Sensitivity tended to increase in summer. There was no correlation between sensitivity to ACh and spontaneous tendency to sweat, except in one subject with congenital absence of sweat glands. Differences in threshold are not due to skin cholinesterase variations.

Intradermal injection of potassium chloride gave no sweat response.

Procaine nerve-block and pre-ganglionic sympathectomy did not affect the response to ACh. No response was obtained 1 year after peripheral nerve section. This may be due to disappearance of specific receptor areas on the cell surface.

The latency of the response to intradermal ACh greatly exceeded the delay after nerve stimulation in man and in the chloralosed cat. This latency could not be reduced experimentally to less than 8 - 10 seconds. Factors which may contribute to the delay are examined.

CHAPTER 111.

ATROPINE AND ANTICHOLINESTERASES.

QUANTITATIVE ASPECTS OF ATROPINE-ACh ANTAGONISM.

Intravenous atropine.

By giving atropine intravenously in repeated small doses it was possible to demonstrate a progressive rise of ACh threshold. In figs. 3 and 4 are set out the results of experiments on two subjects who were given a total of 2.4 mgm. of atropine sulphate by increments of 0.3 mgm. intravenously at 5 min. intervals. The ACh threshold (forearm) was determined after each injection of atropine and the effect on spontaneous palmar sweating was also noted. It was found that spontaneous sweating was completely inhibited before the response to injected acetylcholine 10^{-3} had disappeared.

Intradermal atropine.

Further experiments in which local injections of atropine were given will now be described. At first when atropine and ACh were injected simultaneously, no blocking effect could be demonstrated. By constructing decay curves (e.g. fig.5). I discovered that the effect of atropine was to shorten the response to acetylcholine. Atropine must therefore combine more slowly than ACh

with the sweat gland receptors. (This may well apply to other blocking agents such as TEA - see page 29). Clark (1933) noted that atropine acted more slowly than ACh on the frog heart. In later experiments the atropine was injected first and 15 - 20 minutes was allowed before injecting ACh into the atropinised area. In this way the smallest concentration of atropine was found which would block the threshold concentration of ACh. This was compared with the blocking effect of different concentrations of atropine on thermal sweating induced by heating the feet (Table 17).

At first sight it might appear possible to calculate, from the data in Table 17 and figs. 3 and 4, the concentration of ACh at the neuro-effector junction during thermal and palmar sweating. A moment's reflection will show that we should need to know (1) the amount to which the injected ACh is diluted by tissue fluid before making contact with the receptors: (2) the nature of the differences between stimulation of the glands by nerve impulses and by local injection of ACh. These differences have been discussed in Chapter 11. The most that can be said is that in the subjects tested nervous activity had an effect equivalent to that produced by intradermal injections of 10^{-3} to 10^{-4} acetylcholine.

An observation arising out of these experiments which I am at a loss to explain is the discrepancy between

the dose-response curves of locally and intravenously administered atropine. In an idealised graph (Fig. 6) derived from all the available data on inhibition of thermal and palmar sweating there is a straight-line relationship between I.V. dose and log. local concentration. This applies to other autonomic drugs as well. It is also clear from the fact that 1 mgm. of atropine I.V. will produce roughly the same inhibition as 10^{-5} locally that the drug is concentrated on the cell receptors (since 1 mgm. dissolved in the extracellular fluid or total body water would give a tissue concentration of less than 10^{-7}). Possibly conditions are more favourable for uptake by the receptors when a drug is introduced into the blood stream.

EXPERIMENTS WITH ANTICHOLINESTERASE DRUGS.

Release of ACh by sweat nerve-endings.

Since eserine and neostigmine potentiated the sweat response to injected ACh it was thought that infiltration of an area of skin with an anticholinesterase drug would reveal whether ACh was being released from the sweat nerve-endings a) with the subject at rest in a cool room, b) during the latent period of thermal sweating. A number of experiments were done with neostigmine 10^{-4} before it was realised that this substance has a direct stimulating action on the sweat glands in high concentration (see p.50). In order to prove that the sweating is due to release of

ACh and not to a direct action it is necessary to show that it is prevented by procaine block of the cutaneous nerves. All the observations recorded in Table 18 were made in winter at a room temperature of 18 - 20° C, spontaneous sweating being absent on the forearms. The completeness of the nerve block was subsequently tested by reflex heating. It can be seen that release of ACh at the nerve endings was occurring in several subjects.

It happened that all these subjects were males. Five female subjects were tested in the absence of nerve block; none responded to neostigmine (10^{-6} to 10^{-4}). Of four women who were tested with 10^{-4} eserine three gave no response, and one sweated in July but not in March. The threshold concentrations of neostigmine in two men were 10^{-6} and 10^{-7}. Eserine was used in another male subject and was effective in concentrations down to 10^{-6}; there was no response to 10^{-7}. Since eserine has no direct stimulating action on the sweat glands (p. 50), this is further evidence that in a cool environment transmitter substance may be released from the nerve endings in amounts too small to stimulate the sweat glands. That the ACh is actually released as a result of nerve impulses and does not simply diffuse out of the nerve endings, is shown by the effect of nerve block. The possibility has to be considered that there are cholinergic

endings in the skin other than those supplying the sweat glands, from which the ACh might be released. The existence of cholinergic vasodilator fibres in muscle was demonstrated in the dog by Bülbring & Burn (1935) but they found no positive evidence that such fibres were present in the skin (Bülbring & Burn, 1936[b].)

The release of ACh from the nerve-endings during the latent period of thermal sweating was observed in 2 subjects (fig. 7). It begins about 10 minutes before detectable sweating appears in the untreated areas. The phasic variations characteristic of submaximal sweating (Randall, 1946) are well seen in the neostigmine record. No summation of liberated and injected ACh could be demonstrated. (Table 19).

Measurement of skin cholinesterase.

A preliminary approach was made to the problem of measuring the cholinesterase activity of the skin in situ. The effect of mixtures of ACh and eserine injected intradermally was compared with that of ACh alone, with the object of finding the smallest concentration of eserine needed to produce definite lowering of the ACh threshold. In four out of six subjects 10^{-4} eserine was needed and in the other two 10^{-5} eserine. These concentrations are unexpectedly high, and I suspect that eserine may combine more slowly than ACh with the enzyme (cf. atropine and TEA) so that it cannot easily prevent destruction of ACh when

injected simultaneously. Burgen (1949) found that in vitro eserine combined rather slowly with cholinesterase in the presence of substrate, requiring 10 min. to reach equilibrium.

According to Krayer & others. (1944), the concentrations of eserine required to produce 20% and 80% inhibition of serum cholinesterase in vitro are 10^{-6} and 10^{-5} respectively. If the kinetics of inhibition are similar for the cholinesterase in vivo, one is working within a very narrow range. It would be difficult to say whether a given degree of potentiation was due to partial inhibition of a high concentration of enzyme or complete inhibition of a low concentration of enzyme. As a measurement of cholinesterase activity the maximum potentiation by inhibitors is therefore to be preferred.

The following technique would meet these objections:-

(a) the cutaneous nerves should be blocked with procaine;

(b) a potent, irreversible, cholinesterase inhibitor should be injected intradermally and allowed to act for 15 mins.;

(c) the ACh threshold in the treated area should then be determined and compared with that of untreated skin.

Effect of sympathectomy on skin cholinesterase.

Brücke (1937) found that cholinesterase disappeared

from the sympathetic ganglia of cats after preganglionic nerve section. Preganglionic sympathectomy is not followed by disappearance of skin cholinesterase.
One woman who had been operated on three months previously was subjected to reflex heating. There was no response on the sympathectomised arm. 0.1 cc. of a 10^{-4} solution of the anti-cholinesterase Nu 683 (the dimethyl carbamic ester of 5-phenyl-2-hydroxy-benzyl-trimethylammonium bromide) was injected intradermally. Twenty minutes later 0.01 cc. of 10^{-3} ACh was injected 5cm. away. After allowing time for the response to develop the electrical readings were a) at site of Nu 683 injection - 0, b) at site of ACh injection 0.8 micro-amps., c) half way between the two - 5.0 micro-amps. Starch paper readings corresponded. Hundredfold potentiation of the response to ACh by eserine, tetraethylpyrophosphate and neostigmine was observed in two other subjects on several occasions between three and nine months after preganglionic sympathectomy. It has not been possible to study the skin cholinesterase by this technique after degeneration of the postganglionic fibres since the glands no longer respond to ACh (page 35). The question could be settled by skin biopsy and manometric estimation.

Direct action of anticholinesterases on sweat glands.

It is generally believed that anticholinesterases act by competitive inhibition of the enzyme. If this

is so, they probably have certain structural features in common with acetylcholine and it would not be surprising to find that they were also capable of combining with specific cell receptor groupings to produce direct stimulation of effector organs. This theme has been developed by Koelle & Gilman (1949). Riker & Wescoe (1946) showed that neostigmine had a direct action on striated muscle, and Hobbiger (1950) has demonstrated a direct effect on the frog rectus abdominis muscle.

A direct stimulating action of neostigmine on sweat glands in high-concentration (10^{-4}) was suggested by the finding that procaine nerve block did not prevent the response to intradermal injection. Further evidence was obtained by experiments on sympathectomised subjects, in whom neostigmine 10^{-4} never failed to cause sweating, (Table 20.), although in three of the four subjects there was a negative response to high concentrations of other anticholinesterase drugs. In a concentration of 10^{-4} eserine, Nu 683 and Ro30340 (m-dimethylamino-phenyl-diethylphosphate-methyl-methylsulphate) had no direct action. Tetraethylpyrophosphate (TEPP) 10^{-4} gave no response on one occasion and a small response on another: 10^{-3} caused profuse sweating in two subjects.

SUMMARY.

Data are presented on the quantitative aspects of inhibition by intravenous and intradermal atropine of a) spontaneous sweating, b) sweating produced by intradermal acetylcholine.

In order to prevent the action of ACh by intradermal atropine, the atropine must be injected first and allowed to act for some minutes before the ACh is introduced.

The effects of intravenous and intradermal atropine are compared.

By intradermal injection of low concentration of anticholinesterase drugs it was demonstrated that the release of ACh by the sweat nerve-endings begins some minutes before sweating can be detected when the subject is exposed to external heat. Release of ACh may occur in the absence of sweating even at quite low environmental temperatures (18 - 20°C.). It ceases after procaine nerve block.

Measurement of skin cholinesterase in situ is discussed. This does not diminish after preganglionic sympathectomy. The effect of true denervation of the sweat glands on the skin cholinesterase cannot be measured by an indirect technique.

Neostigmine 10^{-4} and tetraethylpyrophosphate 10^{-3}, injected intradermally, stimulated sweat glands isolated by procaine nerve block or preganglionic sympathectomy.

Eserine, and certain other anticholinesterase drugs, had no such effect in concentrations up to 10^{-4}.

CHAPTER IV.

THE RESPONSE TO ADRENALINE.

Interest in the possible existence of an adrenergic component in the control of sweating has recently been revived by Haimovici (1948) who reported that intravenous dibenamine reduced palmar sweating in man. This was also briefly noted among the effects of dibenamine by Hecht and Anderson (1947) and by Medinets et al. (1948). It had long been known that in certain species e.g. the sheep and the horse, adrenaline injections caused generalised sweating, (Kuno, 1934). Bacq (1932) reported local sweating with intradermal adrenaline in the horse. But since the pharmacological investigation of sweating by Langley, Burn, Dale, Feldberg and others was chiefly carried out on the cat, a species in which the sweat glands happen not to respond to adrenaline, the idea that ACh was the sole chemical transmitter became generally accepted. After the publication of Haimovici's paper, Sonnenschein (1949) investigated the response of human sweat glands to intradermal adrenaline and reported positive results in 21/30 subjects. He got responses with concentrations as low as 10^{-8} from the forearm skin. The response was said to be markedly inhibited by dibenamine and ergotamine but not by

atropine or TEA. (Sonnenschein et al., 1949). Kisin (1948) also reported stimulation of sweat glands by local injection of adrenaline. Sonnenschein's results were confirmed by Wada (1950), who found that 80% of normal Japanese subjects aged 14 - 24 responded to 10^{-7} adrenaline and the rest to 10^{-6}. (He made the interesting observation that the sensitivity of the sweat glands to adrenaline was much less in children and old people. In children under 4 there was usually no response to 10^{-4} adrenaline, except during the first week of life when excitability was about the same as in the mother. This led him to the conclusion that there was some hormone or humoral agent responsible for maintaining the excitability of the sweat glands).

I confirmed that intradermal adrenaline does often stimulate the sweat glands in man and did a number of experiments to investigate the possible physiological significance of this observation. Inhibition of palmar sweating by intravenous dibenamine, a substance with powerful central effects, is of course unacceptable as evidence that adrenaline is actually concerned in the transmission of nerve impulses to the sweat glands. What is needed is the demonstration that spontaneous sweating can be inhibited, by <u>local</u> injection of a selective adrenaline blocking agent. This presented unexpected difficulties. Before describing these experiments

I wish to deal with one or two points about the adrenaline response.

The effect is not due to release of acetylcholine by the adrenaline since it is not prevented by atropine (Table 21).

In Table 22 the smallest effective concentration of l-adrenaline is compared with that of acetylcholine and dl-noradrenaline. 10/12 subjects responded to adrenaline in concentrations of 10^{-3} to 10^{-7}. Allowing for the lower potency of the racemic preparation, the sensitivity to noradrenaline was the same as the adrenaline sensitivity in the six individuals tested. Noradrenaline was tried on the cat's foot pad but, like adrenaline it produced no response while ACh caused profuse sweating. It was suspected that the sensitivity to ACh might vary inversely with the adrenaline sensitivity but this was found not to be the case. It can be seen in Table 22 that the two run closely parallel, which disposes of the attractive hypothesis that in some individuals ACh, in others adrenaline is the principal transmitter to the sweat glands.

The secretion of sweat after adrenaline is prolonged and has been detected more than an hour after the injection. It cannot therefore be due simply to stimulation of the myoepithelial elements since any sweat expressed in this way would evaporate in a few minutes.

The secretory response appears after a latent period of about thirty seconds. Obvious vasoconstriction takes longer to develop. When vasoconstriction is established the amount of sweat secreted becomes very small as judged by the size of the starch paper dots. This is comparable to the effect of obstructing the circulation on thermal sweating (Randall et al., 1948), and recalls the observation of Langley and Uyeno (1922) that the sweat response to pilocarpine on the cat's paw was attenuated by adrenaline.

Ephedrine in a concentration of 3×10^{-3} was tried in two subjects who were sensitive to low concentrations of adrenaline. No sweat response was obtained. This is consistent with the theory that ephedrine acts indirectly by inhibition of amine oxidase (Gaddum & Kwiatowski, 1938), since it is proposed to show that no adrenergic fibres supply the sweat glands. Moreover, potentiation of the sudomotor effect of adrenaline was not demonstrated.

In considering adrenaline blocking agents suitable for injection into the skin dibenamine was at first rejected because of its necrotising property. The first compound tried was Dihydroergocornine (DHO). 0.05 cc. of a 10^{-4} solution was injected intradermally at three sites on the forearm. 15 mins. later adrenaline 10^{-4} gave no response when injected into the treated area, although the response from normal skin was very marked.

Unfortunately the response to 10^{-4} ACh was also markedly inhibited. (Table 23). After reflex heating the treated areas sweated less than the controls. A second experiment was done in which weaker solutions of DHO were used. The response to 10^{-6} adrenaline was completely inhibited by 10^{-5} DHO and partially inhibited by 10^{-6} DHO. 10^{-5} DHO did not diminish the response to 10^{-5} ACh (Table 24). After reflex heating the treated areas sweated equally with the control areas. It will be noted that compared with the first experiment the inhibition of 10^{-4} adrenaline by 10^{-4} DHO was less complete and that the depression of thermal sweating by DHO 10^{-4} did not occur on this occasion.

Since I felt that these results were inconclusive I tested a number of other compounds for their ability to block the adrenaline response selectively. The inhibitory effect of Dihydroergocristine (DCS) was, if anything, weaker than that of DHO (Table 25). N,N-dibenzyl-beta-chloroethylamine hydrochloride (dibenamine) 5% in alcohol propylene-glycol, was allowed to act for 5 mins. after injection of 0.05 cc. There was no inhibition of the response to 10^{-5} adrenaline (Table 26). Various dilutions of this preparation in saline were also ineffective. (5% dibenamine was slightly painful on injection and a tender lump appeared later). Piperidyl methyl benzodioxane (933F) 10^{-3} X 0.1 cc. was also tried and had no inhibitory

effect (Table 27). Finally 2-benzyl-imidazoline hydrochloride (Priscol) was tested: 3 mins. after injection of 10^{-2} X 0.05 cc. the sweat response to adrenaline 10^{-3} was almost completely absent (Starch 4 compared with over 100), and there was no vasoconstriction. Later the blocking effect was demonstrated in another subject. (Table 28). Thermal sweating was enhanced by Priscol 10^{-2}, probably owing to the vasodilator effect.

There is therefore no evidence from experiments with DHO and Priscol for an adrenergic component in thermal sweating. Another line of evidence is the effect of atropine. It is easy to show that atropine totally suppresses sweating due to reflex heating in concentrations as low as 10^{-6}. In the subject shown in fig. 8, who happened to be a West Indian, the contrast between sweating and non-sweating areas after dusting with Quinizarine powder is not very good, but it can be seen that the atropine-treated areas are dry while the DHO areas sweat equally with the controls. No electrical reading was obtained over the atropinised areas, the controls reading 4 - 8 micro-amps. Total suppression of thermal sweating by oral, intravenous and local atropine has been observed on many occasions in different subjects. Since the response to adrenaline is not inhibited by atropine, it is concluded that the only transmitter involved in thermal sweating is acetylcholine.

Emotional sweating was separately investigated. It is significant that although palmar sweating was usually inhibited by intravenous Dibenamine, it was not abolished in those subjects who vomited (Haimovici, 1950). This strongly suggests that any inhibitory effect is due to a central action. Although it is not true, as Sonnenschein et al. (1949) suggest, that the palmar sweat glands cannot be stimulated by local injection of adrenaline (Table 29), there is no evidence that adrenaline is concerned in the transmission of impulses to these glands. In five normal subjects atropine 5 X 10^{-4} was introduced into the palm by iontophoresis (1 - 2 M A /Cm^2 for 10 mins.). Spontaneous sweating was completely suppressed in every case. Similar introduction of DHO had no such effect. Mental arithmetic and sudden loud noises increased sweating in the control and DHO areas but no sweating appeared on the atropinised area. A similar result was obtained from the plantar sweat glands in a case of hyperhidrosis. Another hyperhidrotic subject was studied after suppresion of spontaneous sweating by procaine block of the median nerve at the wrist (Table 30). Atropine 10^{-5} (0.02 cc.) and DHO 10^{-5} (0.02 cc.) were each injected at two sites on the anaesthetic palm. There was no response to 10^{-5} ACh in the atropinised skin; adrenaline 10^{-4} gave a marked response. Before the DHO area could be similarly tested the nerve block wore off and sweating returned,

reaching control levels on the DHO areas although the second atropine area remained dry. The excessive sweating was relieved in this case by small doses of atropine by mouth.

These observations prove that adrenergic nerves are not concerned in thermal and emotional sweating. It is perhaps surprising that glands which are capable of responding to adrenaline should not be stimulated by local diffusion of transmitter from closely adjacent vasoconstrictor terminals. Hillarp (1949) partially denervated salivary glands, then studied them histologically after prolonged nerve stimulation. He found highly active cell complexes (as judged by their granule and vacuole content) side by side with relatively inactive acini. This sharp localisation of transmitter at cholinergic endings may be achieved by a high concentration of cholinesterase, but since the enzymatic inactivation of adrenaline is relatively slow it seems likely that local diffusion of transmitter is limited by some other mechanism.

The work of Armstrong (1935) on the Fundulus heart showed that sensitivity to ACh is only acquired by cells after they have received their innervation. The development of sensitivity is probably associated with the appearance of specific receptor areas at those points on the cell surface with which the nerve terminals make contact. It seems unlikely that sensitivity to adrenal-

line is acquired in this way. However denervation of the sweat glands results in loss of the response to adrenaline and noradrenaline as well as to acetylcholine (Janowitz & Grossman, 1950).

The possibility that circulating adrenaline might sometimes cause sweating was next examined. A subject who responded to 10^{-7} adrenaline intradermally was given an intravenous infusion of adrenaline by a constant speed infusion apparatus. Ascorbic acid was added to the solution to delay oxidation. The rate of infusion was 10 microgrammes/min. for the first 7 mins. then 15 microgrammes/min. for 3 mins. Although pallor, transient tachycardia and an increased pulse pressure were noted there was no increase of sweating on the palms, forearms or forehead. This was perhaps not surprising in view of the difficulty of stimulating the sweat glands with intravenous infusions of ACh and mecholyl. Intra-arterial injection of adrenaline was then tried in the same subject, 20 microgrammes in 2 cc. being rapidly injected into the brachial artery. Blanching of the hand developed 1 - 2 minutes after the injection and there were just appreciable systemic effects. The skin resistance was measured at marked sites on the forearms, palms and fingertips (Table 31). After the injection there was a transient fall of resistance on <u>both</u> forearms except the area previously treated with atropine (10^{-5},

0.1 cc. 20 mins. before). This was attributed to a sensory reflex effect. There was no significant change in the readings from the palms and fingertips. The readings which appeared on the atropinised areas after the injection continued to increase while readings on other sites were falling, and must have been due to the gradual disappearance of atropine from the skin. Intra-arterial injection was repeated in another subject whose sweat glands responded to 10^{-5} adrenaline intradermally. It was confirmed that this local response was not blocked by atropine. 18 microgrammes of adrenaline were injected into the brachial artery, producing coldness and marked pallor of the forearm and hand, with diminution of the radial pulse and slight systemic effects. Pilomotor stimulation was obvious. There was no increase of sweating on the control areas, and two sites which had previously been treated with atropine remained dry.

It was therefore impossible to demonstrate stimulation of the sweat glands in man by intravenous or intra-arterial injection of adrenaline even in individuals who were highly sensitive to the sudomotor effect of local adrenaline injections. The two situations where adrenaline (or noradrenaline) sweating might occur spontaneously are a) in cases of phaeochromocytoma where sweating is sometimes a feature of the attacks: b) in hypoglycaemia. I have not had an opportunity to investigate

a proved case of phaeochromocytoma. A 50 year old man, with diabetes and sustained hypertension, suffered from attacks of sweating with abdominal discomfort, rise of blood pressure, lacrimation, salivation and parotid swellings, the provisional diagnosis being diencephalic autonomic epilepsy. The sweating was found to be inhibited by local injection of atropine. He discharged himself before the effect of intravenous benzodioxane (933 F) on the hypertension (Goldenberg et al., 1947) could be tried. Several other hypertensive patients have been tested with this substance but so far none has shown a fall of B.P. and no tumour has been found in those subjected to laparotomy. With the development of methods for the estimation of adrenaline and noradrenaline in the
E/ urine (Lund,1950, v. Euler,1950), it should become easier to detect cases of phaeochromocytoma.*

Profuse sweating often occurs during insulin hypoglycaemia. Through the kindness of Mrs. Doniach of the Courtauld Institute of Biochemistry I was able to show that this type of sweating is inhibited by local injection of atropine. This means that it is due to cholinergic nerve impulses and not to circulating adrenaline.

* See also Engel A. & von Euler U.S.(1950),Lancet,2,387.

SUMMARY.

Adrenaline and noradrenaline stimulated the sweat glands in man (but not in cats) when injected intradermally. The response was not inhibited by atropine. Individual sensitivity to ACh, adrenaline and noradrenaline was of the same order.

There was no response to ephedrine.

Prior intradermal injection of Priscol or hydrogenated ergot derivatives inhibited the adrenaline response. Benzodioxane (933F) and Dibenamine did not.

Thermal and emotional sweating was completely inhibited by atropine in normal and hyperhidrotic subjects. Dihydroergocornine and Priscol had no such effect. It is concluded that the sweat glands have no adrenergic innervation.

Intravenous and intra-arterial adrenaline failed to cause sweating in subjects who responded well to intradermal adrenaline.

Profuse sweating during insulin hypoglycaemia was abolished by atropine and was therefore not due to circulating adrenaline.

Circulating adrenaline or noradrenaline might be the cause of sweating in cases of phaeochromocytoma.

CHAPTER V.

HYPERHIDROSIS.

There are several clinical conditions of which hyperhidrosis is a feature. A case of probable diencephalic autonomic epilepsy (Penfield 1929) with paroxysms of sweating has already been mentioned. A rather similar case, in which disturbances of temperature regulation also occurred, showed the radiological features of agenesis of the corpus callosum, a diagnosis which was later confirmed at post-mortem. Drenching sweats may occur in paraplegics (Head & Riddoch 1917: Richter & Shaw, 1930: List & Pimenta, 1944), due to a spinal reflex initiated by nociceptive stimuli or visceral distension.

A case of unilateral frontal hyperhidrosis was described by Tarlov & Herz (1947). The disturbance was precipitated by unpleasant thoughts or excitement. In two such cases seen by us, the sweat response to thermal stimulation was also excessive on the affected area.

Another curious variety of hyperhidrosis occurs on the face and head in response to the presence of food in the mouth (Haxton, 1948[a]). Any highly flavoured substance may elicit the response, especially acid material such as apple and vinegar. Haxton calls the

syndrome "Gustatory Hyperhidrosis" and points out that the response normally occurs only after eating spicy food, like curry. Some individuals have an idiosyncrasy to chocolate - Claude Bernard for one - and others sweat after eating cheese or marmalade. (This must be the explanation of the "marmalade steamers" Commander Campbell used to describe on the Brains Trust). An excessive response has been described in syringomyelia and encephalitis, after suppurative parotitis or injuries to the parotid region (auriculo-temporal syndrome) and after division of the cervical sympathetic. In the auriculo-temporal syndrome flushing and sweating occur in the pre-auricular region in response to the presence of food in the mouth. Uprus and co-workers (1934) attributed it to abnormal regeneration following nerve injury, and compared it with the "crocodile tears" seen after facial nerve lesions. But Langenskiold (1946) claimed that the glands on the affected side had been sensitised to ACh.

Gustatory hyperhidrosis after cervical sympathectomy is not uncommon. (13 out of 36 cases in Haxton's series). Several workers have reported that there is an excessive response to local injection of parasympathomimetic drugs on the affected side (Haxton, 1948[a]; Wilson, 1936; List & Peet, 1938[d]). It has been suggested that the sensitised glands might be stimulated by ACh diffusing from the salivary nerve-endings. This would hardly account for

sweating on the forehead. Wilson (1936) described a case (case 3 in his series), in which, after removal of the superior cervical ganglion, the glands on the forehead responded to gustatory but not to reflex thermal stimulation. The sweating was completely abolished by atropine and by supraorbital nerve block. Unless one postulates diffusion from cholinergic vasodilator or motor nerve endings, the only possible conclusion is that these glands had a double nerve supply a) through the cervical sympathetic, transmitting impulses from the thermo-regulatory centre; b) through the fifth nerve. Since Wilson's patient had had the sensory root of the fifth nerve divided as well as having the superior cervical ganglion removed these accessory fibres after leaving the brain stem must have an independent course before joining the 5th nerve distal to the sensory root. They had no connection with the thermal sweat centre.

Cause of essential hyperhidrosis.

The investigations to be described have been confined to the condition known as "essential hyperhidrosis" (Haxton, 1948[b]: Boyd & Jepson, 1950) in which the excessive sweating occurs on the palms and soles, i.e. those areas responding to emotional rather than thermal stimuli. Several of our patients also had acrocyanosis - cold, blue, puffy hands and feet. The association of cold sweaty extremities with anxiety is well known (Wood, 1941),

and at first sight there appears to be a strong presumption that the cause lies in the central nervous system rather than at the periphery. But it would be quite easy to match a group of hyperhidrotic subjects with a normally sweating control group in which the incidence of psychological disorders was identical - a point often overlooked in considering "psychosomatic" diseases. Nor can the fact that the hyperhidrosis is abolished by sleep and thiopentone narcosis (Boyd & Jepson, 1950) be accepted as proof that no peripheral abnormality is present.

I examined the sensitivity of the palmar sweat glands to locally injected acetylcholine in 6 subjects with hyperhidrosis and 8 normal controls in whom the median nerve had been blocked at the wrist with 4% procaine. The ACh threshold varied over a wide range in both groups, from 10^{-4} to 10^{-8} in the hyperhidrotic subjects and from 10^{-3} to 10^{-8} in the controls (Table 32). This seemed to exclude an increased excitability of the glands as a cause of the abnormality. Later it occurred to me that the "threshold" sensitivity might be misleading and that the slope of the dose-response curve might be different in the two groups. I therefore re-examined my results and found that though the data on this point were incomplete, at least two of the control subjects had over 60 glands in action after the injection of

10^{-5} ACh, a greater number than was seen in any of the abnormal subjects with this concentration.

Possible mechanisms of autonomic overactivity may be tabulated as follows:-

1. Nervous - a. Central.
   b. Ganglionic.
   c. Nerve-ending (Excessive release of transmitter).
2. Local deficiency of cholinesterase.
3. Hypersensitivity of tissue receptors.

It is considered that the results quoted above exclude mechanisms 2 and 3 in the case of hyperhidrosis. The one peripheral abnormality which has not been ruled out is excessive release of ACh by the nerve-endings

Electrical stimulation of the peripheral cut end of the lumbar sympathetic chain was tried in one case of thrombo-angiitis obliterans at operation. Sweating and vasoconstriction of the foot were obtained with 8 volts at 25/sec. It would be practicable to implant an electrode for 24 hours, so as to allow time for recovery from the anaesthetic before measuring the response. Knowing the sensitivity of the sweat glands to ACh and the magnitude of the response to a given stimulus in hyperhidrotic and control groups, it should be possible to say whether there is an excessive release of transmitter in hyperhidrosis. Alternatively, if local injection of ACh is not accepted as a valid method

of testing the "sensitivity" of the glands (see p.42), the nerve stimulation technique would give information about the peripheral mechanism as a whole.

The treatment of choice in severe cases of essential hyperhidrosis is sympathectomy (Roberts, 1934: Adson, Craig & Brown, 1935: Telford, 1938: Palmer, 1947: Haxton, 1948[b]). There is no tendency to clinical relapse as in Raynaud's disease, although some return of sweat function eventually occurs (Barcroft & Hamilton 1948[a,b]). Presumably the new nerve pathway is functionally less efficient than the old (Neumann et al., 1943).

The non-surgical management of hyperhidrosis consists in the local use of formalin solutions and astringent lotions, irradiation (which is condemned by most authorities), and the administration of atropine by mouth. Since atropine only inhibits sweating in doses which also inhibit other secretions (Table 33) it is poorly tolerated by most patients. Moreover, atropine does not block the adrenergic impulses responsible for the concomitant acrocyanosis, where this is present. Recently Grimson and co-workers (1950) have reported the successful treatment of hyperhidrosis with the new parasympatholytic drug beta-diethylaminoethyl xanthene-9-carboxylate methobromide (banthine). Side effects included dilatation of the pupil, dryness of the

mouth and constipation.

Theoretically, a ganglionic blocking agent should be particularly useful in the acrocyanosis-hyperhidrosis syndrome since it would inhibit both adrenergic and cholinergic nerve impulses. Until recently the only compounds available have been the quaternary ammonium salts. Apart from postural hypotension, these substances produced other unpleasant effects, such as sensations of coldness and prickling in the hands and feet and loss of visual accommodation; they may cause curariform paralysis (Graham, 1950); and their duration of action is short. Pentamethonium (C.5) and hexamethonium (C6) salts produce a longer-lasting ganglionic blockade with fewer side effects (Paton & Zaimis, 1948[a,b]; Burt & Graham, 1950). Provided these drugs will inhibit sweating without causing postural hypotension, they should prove useful in the control of hyperhidrosis. Smith(1950) reported that C6 in doses of 500 mgm. orally B.D. reduced acid secretion and gastric motility in cases of peptic ulcer but produced serious cardiovascular effects in 2/3 of subjects. Paton (1950) suggested that this type of ganglionic blocking agent might be more effective in states of of abnormally high activity of the autonomic ganglia: thus, in hyperhidrotic subjects, the sweat nerve pathway might be more easily blocked than, say, the splanchnic vasoconstrictor pathway.

Observations have been made with intravenous pentamethonium bromide in 4 cases of hyperhidrosis and in one normal subject. All were females. The results are shown in Tables 34-37 and Fig.9. Two injections of 10 mgm. each were given with an interval of 10 - 15 minutes between them. After the second injection postural faintness occurred in only one subject (A.E. Table 38) and was over while depression of sweating was still maximal. A definite effect on sweating was apparent after the first 10 mgm. in this case; in the others (including the normal control) it was doubtful with 10 mgm. but definite with 20 mgm. There was a tendency for the feet to be more affected than the hands (Fig. 9), a point also noted by Burt & Graham. Vasodilatation in the hands and feet accompanied the inhibition of sweating in most cases. Well marked vasoconstriction developed in the hands in the normal control (Table 34). Unfortunately the feet were not examined in this subject, but it is reasonable to assume that the vasoconstriction in the hands was a compensatory phenomenon accompanying vasodilatation in the lower limb, the ganglia of the upper limb continuing to transmit impulses from the vasomotor centre after those of the lower limb had ceased to function. In one subject (A.E. Table 36) there was a greater effect on the right hand and foot than on the left.

These results show that it is possible to inhibit sweating with intravenous pentamethonium without producing unpleasant side effects. It was therefore decided to try pentamethonium bromide by mouth in the four hyperhidrotic subjects. The drug is dispensed in the form of syrup, since it is too hygroscopic to make a satisfactory tablet. The initial dose was 50 - 100 mgm. B.D. In two subjects (J.S. and G.S.) satisfactory clinical results were obtained with 150 mgm. B.D. A third subject (A.E.) required 250 mgm. B.D. and is now taking tablets of hexamethonium bromide in the same dose with good effect. The oral dose cannot be predicted from the response to intravenous pentamethonium, since subject A.E. was particularly sensitive to the effects of the drug in the preliminary (I.V.) test. No side effects were noted in these three patients. Suppression of sweating and of vasoconstriction tended to be more complete in the feet than in the hands. The fourth subject (S.C.) complained of headaches when taking 150 mgm. B.D. As she was a frequent sufferer from headache an inert mixture was substituted without her knowledge. The headaches persisted.

The total period of observation in these cases is still only 4 - 6 weeks. A longer period will have to elapse, and more cases will have to be studied, before the value of methonium compounds in hyperhidrosis can be finally assessed.

SUMMARY.

The clinical varieties of hyperhidrosis are reviewed.

Possible mechanisms of essential hyperhidrosis are discussed. The palmar sweat glands were not hypersensitive to intradermal ACh in six hyperhidrotic subjects as compared with a control group. More complete information about the peripheral mechanism could be obtained by nerve-stimulation experiments.

The treatment of hyperhidrosis is considered, with special reference to the use of methonium compounds. Promising results have been obtained in a few cases with oral pentamethonium and hexamethonium bromide.

CONCLUSIONS.

Detailed summaries are provided at the end of each chapter. The main conclusions are given below.

1) The sensitivity of sweat glands to intradermally injected acetylcholine (ACh) does not correlate well with spontaneous tendency to sweat.

2) Sensitivity to ACh is lost after degeneration of the post-ganglionic nerve fibre. Preganglionic sympathectomy does not affect the response.

3) After intradermal injections of ACh there is an unexplained delay of not less than 10 seconds before sweating is detectable.

4) When injected intradermally atropine is taken up by the receptors more slowly than ACh. This relationship also applies to the inhibition of the action of nicotine by tetraethylammonium bromide.

5) Release of ACh by the sweat nerve endings during reflex heating can be detected some minutes before sweating occurs. It may also occur in the absence of sweating at quite low environmental temperatures (18 - 20°C.).

6) In most persons intradermal adrenaline can also stimulate sweat secretion, although there is evidence from experiments with blocking agents that the innervation of the sweat glands is purely cholinergic.

7) There is no evidence that in hyperhidrotic subjects the overactive palmar sweat glands are hyper-sensitive to ACh.

8) Oral administration of ganglionic blocking agents of the methonium group is a promising method of treatment in hyperhidrosis.

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APPENDIX.

Tables 1 - 37.

Figures 1 - 9.

Table 1.

EFFECT OF DEPTH OF INJECTION ON RESPONSE TO ACETYLCHOLINE (ACh.)

Site of injection	T.M.C.		C.A.K.	
	Starch paper	Micro-amps	Starch paper	Micro-amps
Superficial intradermal	-	-	6	0.4
Deep intra-dermal	20	1.5	6	0.4
Subcutaneous	26	2.2	6	0.6
Intramuscular	0	0	-	-

In this table and in subsequent tables the words -

Starch paper = number of dots on starch paper applied to iodine-treated skin.

Micro-amps = amount of current passing through skin.

and the symbols -

0 = No response.

- = No observation.

Except where otherwise stated injections were made into the flexor surface of the forearm.

Table 2. SUBJECT A.C.P.

RESPONSES TO INTRADERMAL MECHOLYL 10^{-3} (0.01cc) INJECTED INTO TWO COMPARABLE SITES ON EACH FOREARM.

Minutes after injection	Right forearm		Left forearm	
	Starch paper	Micro-amps.	Starch paper	Micro-amps.
1	37	4.0	3	0.3
5	-	7.0	-	0.8
7	-	11.5	-	1.0
15	-	8.5	27	2.2
30	-	7.0	-	2.4
42	-	1.2		1.0
50	0	0.3	0	0.2
62	-	0	-	0
2	50	4.0	22	0.9
6	-	8.8	-	2.4
10	-	12.0	-	3.2
24	-	8.2	-	6.1
36	-	4.0	-	3.0
44	-	3.4	-	2.2
56	0	0.7	0	0.7

Table 3. RESPONSES TO INTRADERMAL ACh. ON THE TWO FOREARMS.

SUBJECT	INJECTION	RIGHT FOREARM		LEFT FOREARM	
		STARCH PAPER	MICRO-AMPS.	STARCH PAPER	MICRO-AMPS.
R.B.R.R.	ACh. 10^{-5}	0	0.1	0	0
	10^{-4}	0	0	0	0
	10^{-3}	2	0.9	10	1.8
J.K.	ACh. 10^{-7}	0	0	0	0
	10^{-5}	0	0.4	0	0.05
	10^{-4}	19	1.7	11	1.4
J.A.F.	ACh. 10^{-5}	0	0	0	0
	10^{-3}	0	0	0	0
	5×10^{-3}	-	0	-	0.8
	4×10^{-3}	-	2.0	-	0.1
	3×10^{-3}	-	0.5	-	1.5
	2×10^{-3}	-	0.4	-	0
	10^{-2}	47	1.7	37	3.0
N.W.F.H.	ACh. 10^{-5}	0	0.3	0	0.1
	10^{-4}	0	0.6	0	0.1
	10^{-3}	27	1.6	34	2.7
A.C.P.	ACh. 10^{-7}	0	0	0	0
	10^{-5}	0	0	0	0
	10^{-4}	2	0.05	0	0
	10^{-3}	23	3.8	5	0.7
I.G.H.	ACh. 10^{-7}	-	0.1	-	0.1
	10^{-5}	-	0.1	-	0.1
	10^{-4}	-	0.2	-	0.2
	10^{-3}	-	0.7	-	0.9
	10^{-2}	-	3.0	-	3.0

Table 4. COMPARISON OF ACh THRESHOLDS ON PALM AND FOREARM.

SUBJECT	PALM	FOREARM
I.S.	10^{-7}	10^{-5}
A.C.P.	10^{-4}	10^{-5}
A.A.G.L.	10^{-5}	10^{-5}
G. du B.	10^{-5}	10^{-4}
J.R.	10^{-7}	10^{-5}
B.A.S.	10^{-8}	10^{-6}
G.P.B.	10^{-7}	10^{-6}
J.A.F.	10^{-7}	10^{-5}
I.G.H.	10^{-3}	10^{-3}
B.F.	10^{-4}	10^{-5}
S.C.	10^{-6}	10^{-5}
G.L.S.	10^{-7}	10^{-5}
G.R.S.	10^{-5}	10^{-5}
T.M.C.	10^{-8}	10^{-7}

ACh threshold = smallest effective concentration of intradermally injected Acetylcholine which produced sweating.

Table 5. SUBJECT T.M.C. COMPARISON OF DILUTIONS OF ACh. PREPARED a) with a series of syringes, b) with a series of pipettes and flasks, ON HUMAN SWEAT GLANDS.

SUPPOSED CONC'N OF ACh.	MINUTES AFTER INTRADERMAL INJECTION	SYRINGE		PIPETTE & FLASK		UNINJECTED SKIN micro-amps.
		STARCH PAPER	μA	STARCH PAPER	μA	
10^{-8}	2	-	1.1	-	0.5	0.1
	4	6	1.2	-	0.8	
	6	-	1.0	-	1.0	
	9	-	-	2	0.8	
	14	-	0.1	-	-	
10^{-10}	2	-	0.2	-	0.1	0.1 - o.2
	5	-	0.2	-	0.1	0.1 - 0.2

Table 6. COMPARISON OF IODINE-STARCH PAPER AND ELECTRICAL READINGS AFTER INTRADERMAL INJECTIONS OF ACh, MECHOLYL AND ADRENALINE

SUBJECT	STIMULUS	STARCH PAPER (No. of dots)	CURRENT Micro-amps.	VASO-CONSTRICTION
R.V.S.	ACh 10^{-5}	0	0	-
	10^{-4}	8	1.6	
	10^{-3}	15	2.0	
W.R.	ACh 10^{-6}	0	0	-
	10^{-5}	3	0.2	
	10^{-4}	11	1.0	
A.C.P.	MECHOLYL 10^{-7}	0	0.2	-
	10^{-6}	2	0.5	
	10^{-5}	7	0.7	
	(REPEAT) 10^{-5}	9	1.0	
M.K.M.	ADRENALINE 10^{-6}	0	0	ABSENT
	10^{-5}	0	0	ABSENT
		Later 0	0.6	JUST VISIBLE
	10^{-4}	3	0.5	ABSENT
		Later 1	4.0	MARKED
	10^{-3}	10	2.0	SLIGHT
		Later 0	8.0	MARKED

Table 7. Subject J.K.

EFFECT OF INTRAVENOUS ATROPINE (0.5 + 0.5 mg.) ON MECHOLYL THRESHOLD AND SALIVARY FLOW.

TOTAL DOSE OF ATROPINE	CONCEN'N OF MECHOLYL	SWEATING		SALIVATION (GM/4 MINS.)
		Starch paper	Micro-amps	
Nil	10^{-10}	1	0.3	
	10^{-9}	6	1.8	1.2 - 1.45
	10^{-8}	5	2.2	
0.5 mgm.	10^{-10}	-	0.1	1.25
	10^{-9}	3	0.8	
1.0 mgm.	10^{-7}	-	0	0.35
	10^{-6}	-	0.5	
	10^{-5}	12	2.2	

Saliva was collected by expectoration in 4 - minute periods. An interval of 3 minutes was allowed between successive collection periods.

Table 8. SUBJECT W.F.F.

EFFECT OF ATROPINE ON RESPONSE TO INTRADERMAL ACh.

TIME	ATROPINISED AREA	NORMAL SKIN micro-amps.	CONTROL (uninjected)
5.18 p.m	INJECTION	INJECTION	-
5.19	0	7.8	0
5.20	0	10.0	0
5.25	0	5.4	0
5.33	0	0.9	0

Atropine Sulphate 6 x 10^{-4} introduced into skin by iontophoresis (1 MA/SQ.CM/10 mins.) at 5.00 p.m. At 5.18 p.m. injection of ACh 10^{-4} x 0.01 ml.

Table 9. Subject I.S.

EFFECT OF 10^{-3} TETRAETHYLPYROPHOSPHATE (T E P P) ON THE RESPONSE TO INTRADERMAL ACh.

INJECTION	With TEPP		Without TEPP	
	Starch paper	Micro-amps	Starch paper	Micro-amps
ACh 10^{-7}	4	0.5	-	-
10^{-6}	13	1.2	0	0
10^{-5}	-	-	3	0.2
10^{-4}	-	-	11	1.0

0.1 cc. TEPP was injected 5 mins. before the injection of ACh.

Table 10. RELATIVE POTENCY OF ACh and MECHOLYL

	SUBJECT	ACh THRESHOLD	Mecholyl THRESHOLD
MALES AGED 19-22	J.K.	10^{-5}	10^{-9}
	N.F.W.H.	10^{-4}	10^{-9}
	J.K.L.	10^{-5}	10^{-7}
	D.L.C.	10^{-5}	10^{-8}
	I.G.H.	10^{-3}	10^{-7}
	A.C.P.	10^{-3}	10^{-5}
FEMALES AGED 16-25	A.M.	10^{-4}	10^{-6}
	G.E.M.	10^{-3}	10^{-5}
	M.C.H.	10^{-4}	10^{-4}
	A.H.G.	10^{-3}	10^{-5}
	V.R.	10^{-2}	10^{-5}
	A.M.E.	10^{-3}	10^{-5}
	M.S.G.	10^{-4}	10^{-4}

Table 11.

DISTRIBUTION OF ACh THRESHOLDS (FOREARMS) IN NORMAL YOUNG ADULTS.

ACh THRESHOLD	MALES (25)	FEMALES (25)	TOTAL (50)
10^{-7}	1	0	1
10^{-6}	3	2	5
10^{-5}	11	8	19
10^{-4}	6	7	13
10^{-3}	4	6	10
10^{-2}	0	1	1
No response to 10^{-2}	0	1	1

Table 12.

EFFECT OF HYALURONIDASE ('HYALASE') ON THE RESPONSE TO INTRADERMAL ACh.

SUBJECT	INJECTION	Without 'HYALASE'		With 'HYALASE'	
		Starch paper	Micro-amps	Starch paper	Micro-amps.
M.K.M.[1]	ACh 10^{-6}	0	0	0	0
	10^{-5}	0	0.4	20	6.0
	10^{-4}	20	4.0	-	-
M.K.M.[2]	ACh 10^{-7}	0	0	0	0
	10^{-5}	1	0.8	25	9.0
M.J.P.[3]	ACh 10^{-6}	0	0	0	0
	10^{-5}	1	0.5	22	6.0
	10^{-4}	12	1.8	-	-

1 = 'Hyalase' & ACh injected simultaneously

2,3 = 'Hyalase' injected 5 - 10 mins. before ACh.

Table 13. SEASONAL CHANGES IN ACh THRESHOLD (FOREARM)

SUBJECT	NOVEMBER TO JANUARY	MARCH	JULY TO AUGUST
G.L.S.P.	10^{-5}	-	10^{-6}
G.M.	a) 10^{-3}, b) 10^{-3}*	-	10^{-5} 10^{-5} 10^{-5}
I.G.H.	10^{-3}	10^{-3}	-
J.A.F.	10^{-3}	10^{-5}	-
V.R.	10^{-2}	-	10^{-3}
D.H.H.	No response to 10^{-2}	-	10^{-3}

* a) 1949. January.

b) 1949. November.

Table 14. EFFECT OF INTRADERMAL NICOTINE ON SWEAT GLANDS. BLOCKING BY INTRADERMAL TETRAETHYLAMMONIUM BROMIDE. (T.E.A.B.)

SUBJECT	INJECTION	STARCH PAPER	μA
G. du B.	10^{-5} x 0.01 cc.	-	0
	10^{-4} x 0.01	-	0
	10^{-5} x 0.05	-	0
	10^{-5} x 0.10	-	0
	10^{-5} x 0.15	-	0
J.H.	A. 10^{-5} x 0.05	over 100	20
	B. 10^{-5} x 0.05	0	0·05

A = before T.E.A.B.

B = 8 mins. after intradermal injection of 0.15 cc. of T.E.A.B. 10^{-2}

Table 15.

EFFECT OR PROCAINE NERVE BLOCK ON SENSITIVITY TO INTRADERMAL MECHOLYL & ACh.

	SUBJECT	NORMAL SKIN	ANAESTHETISED SKIN.
Mecholyl threshold	A.C.P.	10^{-5}	10^{-6}
	I.G.H.	10^{-7}	10^{-7}
	D.L.C.	10^{-8}	10^{-9}
	J.A.F.	10^{-3}	10^{-3}
ACh threshold	T.M.C.	10^{-7}	10^{-7}
	S.C.	10^{-6}	10^{-5}

Cutaneous nerves to the forearm located below the elbow by faradism and blocked with 4% procaine. Completeness of block tested by reflex heating.

Table 16. EFFECT OF PREGANGLIONIC SYMPATHECTOMY ON ACh. THRESHOLD IN FOREARM.

(8 LIMBS IN 5 SUBJECTS)

SUBJECT	BEFORE OPERATION	5 - 14 days after operation.	14 days to 3 months after operation.	6 to 12 months after operation.
I.S.	10^{-6} -	10^{-5} 10^{-5}	- 10^{-5}	10^{-6} 10^{-6}
R.H.	10^{-5} -	- 10^{-4}	- -	10^{-5} 10^{-4}
B.A.S.	10^{-4} -	- -	10^{-5} 10^{-6}	10^{-5} 10^{-5}
H.M.	-	-	-	10^{-3}
J.Sch.	-	10^{-4}	-	-

Table 17.

BLOCKING EFFECT OF INTRADERMAL ATROPINE ON SWEATING INDUCED BY LOCAL INJECTION OF ACh AND BY REFLEX HEATING

SUBJECT	NATURE OF STIMULUS	ELECTRICAL READINGS (MICRO-AMPS)				
		WITHOUT ATROPINE	WITH ATROPINE			
			10^{-7}	10^{-6}	10^{-5}	10^{-4}
G.M.	ACh 10^{-5}	0	-	-	-	-
	10^{-4}	1.2	0.7	0.8	0.8	0.1
	HEATING	0.4 - 2.0	0.9	1.0	0.8	0.2
G.du B.	ACh 10^{-3}	6.0	7.0	0	0	0
	HEATING	3.0 - 6.0	3.0	3.0	1.0	0.6
J.F.	ACh 10^{-5}	0	-	-	-	-
	10^{-4}	1.2	1.0	0.4	1.0	0
	HEATING	3.0 - 6.0	3.0	1.5	1.2	0.1
B.A.S.	ACH	Not tested				
	HEATING	2.0	2.0	1.2	0	0

Table 18 EFFECT OF PROCAINE NERVE BLOCK ON THE RESPONSE TO INTRADERMAL NEOSTIGMINE IN A COOL ENVIRONMENT (18 - 20°C)

SUBJECT	CONCENTRATION of NEOSTIGMINE	SWEATING	
		NORMAL SKIN	ANAESTHETISED SKIN
N.F.W.H.	10^{-6}	+	0
	10^{-5}	+	0
	10^{-4}	+	+
I.G.H.	10^{-5}	+	0
A.C.P.	5×10^{-4}	+	+
O.D.	10^{-5}	0	0
	10^{-4}	+	0
	5×10^{-4}	+	0
D.L.C.	10^{-7}	+	0
	10^{-6}	+	0
	10^{-5}	+	0
	10^{-4}	+	+
J.A.F.	10^{-5}	0	0
	10^{-4}	+	+
T.M.C.	10^{-4}	+	+
S.J.	10^{-4}	+	+
J.K.R.	10^{-6}	+	0
	10^{-5}	+	0
F.H.	10^{-4}	+	+
J.R.	10^{-4}	+	+
A.A.G.L.	10^{-4}	+	+

Table 19. Subject R.B.R.R.

Effect of Reflex Heating on Response to Ach

Time	Concentration of ACh	Electrical Readings (Micro-amps)		Skin Temp. (^{o}F)	
		Injected Area	Uninjected Skin	Forearm	Finger
2.30	10^{-5} 10^{-4} 10^{-3}	0 0.3 1.1	0 - -	30.5 - -	27.5 - -
3.00	Feet in Hot Water				
3.10	10^{-5}	0	0	30.5	23.5
3.20	10^{-5}	0	0	31.0	28.0
3.30	10^{-5}	0	0	32.0	30.0
3.35	10^{-5}	0.3	0.3	33.5	32.5
(Sweating became profuse between 3.35 and 3.45)					
3.45	-	-	3.0	-	-

Table 20

Effects of intradermal injection of anticholinesterase drugs on sweat secretion after preganglionic sympathectomy

	Neostigmine	Eserine	TEPP	Nu 683	Ro 30340
R.H.	+	-	-	-	-
B.A.S.	+	0	+	0	-
A.H. -R.arm	+	0	-	0	-
L.arm	+	0	-	0	-
I.S.	+	-	+	0	0

TEPP = tetraethylpyrophosphate.

Nu 683 = dimethylcarbamic ester of 5-phenyl-2-hydroxylbenzyl-trimethylammonium bromide

Ro 30340 = m-dimethyl amino phenyl diethyl phosphate-methyl methyl sulphate.

All drugs given in saline in a concentration of 10^{-4}, except TEPP (10^{-3} in propylene glycol.) 10^{-4} TEPP gave a minimal sweat response in subject B.A.S. on one occasion and no response on another occasion. 10^{-3} TEPP also caused sweating in two normal subjects =(M.P. and G.L.P.) after the glands had been isolated by procaine block of the cutaneous nerves.

Table 21 Subject G.L.S.P.

Effect of Intradermal Atropine on Response to Adrenaline.

	Without atropine		With atropine	
	Starch Paper	Micro-amps.	Starch Paper	Micro-amps.
Adren. 10^{-4}	100	5.0	60	7.0

Atropine 10^{-4} (0.05 cc.) 20 mins. before Adren.

Table 22.

Threshold concentrations (to produce sweating) of l-adrenaline, dl-noradrenaline and acetylcholine, (Intradermal injection in forearm.)

Subject	l-adrenaline	dl-noradrednaline	Acetylcholine
G.L.S.P.	10^{-7}	10^{-6}	5×10^{-6}
G.M.	10^{-4}	10^{-4}	10^{-4}
E.P.S.	10^{-6}	10^{-4}	10^{-5}
J.O.	10^{-3}	No response to 10^{-3}	10^{-3}
C.A.K.	10^{-3}	10^{-3}	10^{-4}
D.H.H.	No response to 10^{-3}	No response to 10^{-3}	No response to 10^{-2}
A.A.G.L.	10^{-5}	Not tested	10^{-5}
J.M.	10^{-6}	-	10^{-5}
M.K.M	10^{-4}	-	10^{-4}
G.S.	10^{-5}	-	10^{-4}
J.B.L.H.	No response to 10^{-3}	-	10^{-3}
F.H.	10^{-5}	-	10^{-6}

In subject M.K.M mixtures of adrenaline and A Ch. were tried. No potentiation was detected.

Table 23 Subject G.L.S.P

Effect of Intradermal 10^{-4} Dihydro-ergocornine (DHO) on Sweat Responses to acetylcholine and adrenaline and to Reflex Heating

STIMULUS	With DHO		Without DHO	
	Starch Paper	Micro-amps	Starch Paper	Micro-amps.
ACh. 10^{-6}	-	-	0	0
10^{-5}	1	0.6	6	1.7
10^{-4}	4	0.8	42	5.5
Adren. 10^{-6}	0	0	7	1.4
10^{-4}	0	0	40	5.0
Reflex heating	-	2-4	-	6-8

Table 24 Subject G.L.S.P

Effect of Lower Concentrations of Intradermal Dihydroergocornine (DHO) on Responses to Adrenaline, ACh and Reflex Heating.

	Adren 10^{-6}		Adren 10^{-4}		ACh 10^{-5}		Reflex Heating
	Starch Paper	Micro-amps.	Starch Paper	Micro-amps	Starch Paper	Micro amps	
Untreated Skin	30	2.5	over 50	5.0	6	1.2	3-6 micro-amps.
DHO 10^{-6}	4	0.6	20	2.0	-	-	3.5
DHO 10^{-5}	0	0	27	2.0	12	2.0	3.2
DHO 10^{-4}	0	0	25	1.4	-	-	4.5

Table 25 Subject J.M.

Effect of Intradermal 10^{-4} Dihydroergocristine (DCS) on Response to Adrenaline

	With DCS		Without DCS	
	Sweating (Starch Paper)	Vasocon-striction.	Sweating (Starch Paper)	Vasocon-striction.
Adren. 10^{-6}	0	ABSENT	11	PRESENT
Adren. 10^{-5}	22	PRESENT	35	PRESENT

Table 26 - Subject J.M.

Effect of Intradermal dibenamine 5×10^{-2} on the Response to Adrenaline

	With dibenamine			Without dibenamine		
	Sweating		Vasoconstr.	Sweating		Vasoconstr.
	Starch Paper	Micro-amps.		Starch Paper	Micro-amps	
Adren. 10^{-5}	25	2.6	PRESENT	24	3.2	PRESENT

Table 27. Subject G.L.S.P.

Effect of piperidyl methyl benzodioxane (933 F) 10^{-3} on the Response to Adrenaline .

	With 933 F			Without 933 F		
	Sweating		Vasoconstrn.	Sweating		Vasoconstrn.
	Starch Paper	Micro-amps		Starch Paper	Micro-amps	
Adren. 10^{-5}	40	3.0	PRESENT	38	3.0	PRESENT
Adren. 10^{-4}	over 100	6.8	PRESENT	over 100	6.5	PRESENT

Table 28. Subject J.M.

Effect of Intradermal benzylimidazoline (Priscol) on the Responses to Intradermal Adrenaline and to Reflex Heating

	Adren. 10^{-5}		Adren. 10^{-4}		After Reflex Heating
	Starch Paper	Vasoconstr.	Starch Paper	Vasoconstr.	
Untreated Skin	30	PRESENT	44	PRESENT	8-12 microamps.
Priscol 10^{-5}	-	-	40	PRESENT	-
Priscol 10^{-4}	9	ABSENT	37	PRESENT	-
Priscol 10^{-3}	-	-	5	JUST VISIBLE	-
Priscol 10^{-2}	-	-			15 microamps.

Table 29

Stimulation of palmar sweat glands by intradermal adrenaline.

The median nerve was blocked at the wrist with 4% procaine.

	Conc.^{n} of adrenaline	Starch Paper.
G.M.	10^{-6}	50-100
	10^{-4}	over 100
F.J.H.	10^{-6}	7
	10^{-4}	50-100

Table 30

Effect of Intradermal Dihydroergocornine (DHO) and atropine on Palmar Sweat Glands in a Case of Hyperhidrosis (A.E.). The Median Nerve at the Wrist was blocked with Procaine.

	ACh. 10^{-5}		Adfen. 10^{-4}		After nerve block had worn off.
	Starch Paper	Micro-amps.	Starch Paper	Micro-amps	
Atropine 10^{-5}	0	1.5	60	16.0	1.5 micro-amps.
DHO 10^{-5}	-	-	-	-	14 - 16
Control	0	1.5	0	1.5	14 - 16

Atropine was injected at two different sites, only one of which was used for subsequent ACh and adrenaline injections.

Table 31 Subject G.L.S.P.

EFFECT OF INJECTION 20 micro-grammes OF ADRENALINE INTO RIGHT BRACHIAL ARTERY ON SWEATING

(Electrical readings in micro-amps.)

	RIGHT (injected)									LEFT									
	F	P_1	P_2	P_3	1	2	3	4	5	F	P_1	P_2	P_3	1	2	3	4	5	A_1	A_2
BEFORE	0.1	1.0	1.2	1.2	3.0	3.4	3.4	5.5	4.0	0	1.8	3.4	1.8	3.4	3.0	3.8	4.8	5.4	0	0
2 MIN. AFTER	0.6	1.0	1.2	1.6	3.6	3.4	3.8	5.3	3.6	0.5	1.4	2.0	1.0	3.2	2.8	3.0	4.5	4.2	0	0.2
5 MIN. AFTER	0.5	1.0	0.8	1.4	3.2	3.5	3.5	4.5	3.5	0.2	1.2	1.8	1.0	2.5	2.6	2.8	4.4	4.8	0.2	0.8
10 MIN AFTER	0.3	0.8	0.8	1.0	2,8	3.3	3.2	4.8	3.0	0.1	1.0	2.2	1.0	3.0	2.2	2.4	4.4	4.2	0.4	0,9

F = Forearm

P_{123} = 3 sites on palm

12345 = Digits

A 1 2 = Sites of previous atropine injection on right forearm and right palm.

Table 32

Threshold concentration of ACh for stimulation of palmar sweat glands in normal and hyperhidrotic subjects.

Hyperhidrotic Subjects		Normal Subjects.	
B.F	10^{-4}	I.G.H.	10^{-3}
Gr.S	10^{-5}	A.C.P.	10^{-4}
S.C.	10^{-6}	A.A.G.L.	10^{-5}
I.S.	10^{-7}	G.du B.	10^{-5}
Gl.S.	10^{-7}	J.R.	10^{-7}
B.A.S.	10^{-8}	G.P.B.	10^{-7}
		J.A.F.	10^{-7}
		T.M.C.	10^{-8}

The glands were first isolated by procaine block of the median nerve.

Table 33

Effect of intravenous atropine on palmar sweating, salivation and heart rate in a case of hyperhidrosis (B.A.S.)

Total Dose of Atropine	Palmar Sweating	Heart Rate.	Saliva (5-min. collections)
0	over 24 micro-amps	78/MIN	1.70 GM.
0.4 mg.	over 24	82	1.55
0.6	6.0 *	108	0.20
0.8	5.0 *	114	0

* Hands felt dry

Table 34

Effect of Pentamethonium Bromide on Heart Rate, Blood Pressure and Sweating in a Normal Subject (M.K.)

Time	Posture	Heart Rate (Per Min.)	B.P. (mm. Hg.)	Electrical Readings (Micro-amps.)	
				R.Palm	L.Palm.
5.38	Recumbent	80	140/90	21	18
.55		70	115/80	15	19
6.00		74	115/80	8	9
.05		76	115/80	12	20
.07	Pentamethonium Bromide 10 mgm. I.V.				
.09		82	115/70	11	16
.11		80	115/75	6	11
.13		80	115/75	6	11
.15		80	115/75	5	12
.19	Pentamethonium Bromide 10 mgm. I.V.				
.20		80	110/80	11	16
.22		84	110/75	6	9
.24		78	110/75	5	5
.27		78	110/80	2	3
.30		78	110/80	2	8
.31	Sitting	No Symptoms			
.33		92	100/80	16	19
.36		92	105/85	6	8
.40		92	105/85	7	15
.41	Standing	No Symptoms			
.45		100	105/85	14	16

Table 35

Effect of Pentamethonium Bromide on Blood Pressure, Heart Rate and Sweating in a Case of Hyperhidrosis. (J.S.)

Time	Posture	Heart Rate (Per min.)	B.P. (mm.Hg)	Electrical Readings on Palm (Micro-amps.)	
				Right	Left
10.03	Recumbent	96	145/100	24	22
.17		90	145/100	Over 24	22
.25		96	145/100	19	22
.33		86	140/100	15	23
.38		92	145/100	15	15
.39	Pentamethonium Bromide 10 mgm. I.V.				
.41		-	-	Over 24	22
.42		98	145/100	21	21
.44		96	140/95	15	19
.46		96	140/95	12	17
.48		96	140/95	12	17
.49	Pentamethonium Bromide 10 mgm. I.V.				
.51		-	-	16	19
.52		96	135/90	12	16
.54		96	135/95	5.5	15
.56		96	135/95	3.5	12
.58		96	140/100	2.5	9
11.02		96	140/100	2.5	8

Continued overleaf:

Table 35 - Continued

Time	Posture	Heart Rate (Per min.)	B.P. (mm.Hg.)	Electrical Readings on Palm (Micro-amps)	
				Right	Left
11.05	Sitting	120	160/115	4	7.5
.07		120	155/110	2	2
.10		120	155/110	3	3
.12	legs down	124	145/105	5	9
.16		86	135/100	2	8
.20		108	130/100	2	8
.27	Standing	120	140/100	9	12
.38		112	140/105	7	7
12.00		-	-	19	19

No Symptoms.

Table 36

Effect of Pentamethonium Bromide on Heart Rate, Blood Pressure and Sweating in a Case of Hyperhidrosis (A.E.)

Time	Posture	Heart Rate (Per min.)	B.P. (mm.Hg)	Electrical Readings (Micro-amps)			
				Palms		Soles	
				Right	Left	Right	Left
12.15	Recumbent	100	115/65	19	24	-	-
.25		98	105/65	13	20	15	16
.32		100	105/60	14	19	15	18
.34	Pentamethonium Bromide		10 mgm. I.V.				
.35		100	100/55	15	23	18	20
.37		102	100/55	15	22	14	20
.39		96	100/60	12	18	13	19
.41		96	100/65	9	16	11	17
.43		98	100/65	9	19	11	17
.46		94	105/65	12	18	10	16
.48	Pentamethonium Bromide		10 mgm. I.V.				
.49		94	100/65	12	15	7	15
.51		96	95/60	5	12	6	13
.55		94	95/65	4	11	4	12
.56	Sitting	No symptoms.					
.57		110	105/80				
.59		116	100/80	3	14	3	12

Continued overleaf:

Table 36 - Continued

Time	Posture	Heart Rate (Per min.)	B.P. (mm.Hg.)	Electrical Readings (Micro-amps)			
				Palms		Soles	
				Right	Left	Right	Left
1.02	Standing:	Faint and dizzy					
.03		120	50/?				
.06	Walking:	-	50/?	3	11	4	12
.07	Recumbent	No symptoms					
.08			100/60				
.13		92	100/60	1	3	2	10
.15	Sitting	Dizzy.					
.16	Recumbent	No symptoms					
.35		84	100/60	0.5	2.5	2.5	8
.37	Sitting	No symptoms					
.38	Standing	No symptoms					
.39			85/?				
.40			80/?				

Table 37

Effect of Pentamethonium Bromide on Heart Rate, Blood Pressure and Sweating in a case of Hyperhidrosis (G.S.)

Time	Posture	Heart Rate (Per min.)	B.P. (mm.Hg)	Electrical Readings (Micro-amps)			
				Palms		Soles	
				Right	Left	Right	Left
10.10	Recumbent	106	100/60	24	over 24	16	17
.27		102	115/65	11	15	14	12
.30		100	115/65	16	20	15	12
.41		106	120/60	23	over 24	15	13
.44	Pentamethonium Bromide 10 mgm. I.V.						
.46		96	115/65	over 24	over 24	15	12
.48		102	110/65	over 24	over 24	11	10
.50		94	110/60	23	over 24	10	8
.52		92	110/60	21	24	10	8
.54		92	105/60	16	22	9	6
.56		94	105/55	18	20	7	4
.58		94	105/60	16	17	5	4
11.01	Pentamethonium Bromide 10 mgm. I.V						
.02		94	115/65	18	17	12	9
.04		88	110/60	18	16	8	7
.06		92	105/60	11	13	7	4
.09		90	110/65	12	13	4	3
.11	Sitting No Symptoms						
.13		100	105/70	15	12	7	5
.15	Standing No symptoms						
.16		100	110/70	17	12	9	8
.20	Walking No symptoms						
.21		-	-	12	12	-	-

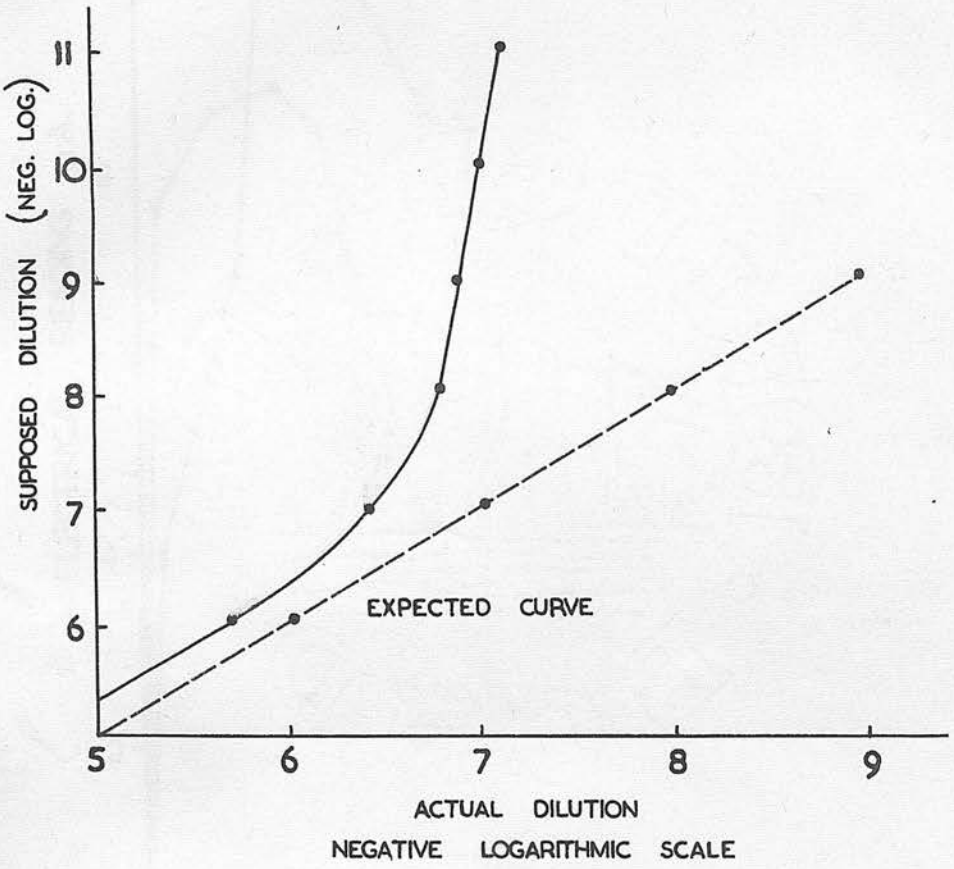


Fig. 1. To show the error involved in making dilutions of Ach with a single syringe (plotted vertically) instead of with separate pipettes. Solutions were compared on the frog rectus abdominis muscle (by Dr. F. Hobbiger) with accurate dilutions made up with a series of graduated pipettes and flasks.

Fig. 2. TIME-COURSE OF RESPONSE TO ACh 10^{-3} AND MECHOLYL 10^{-3}.

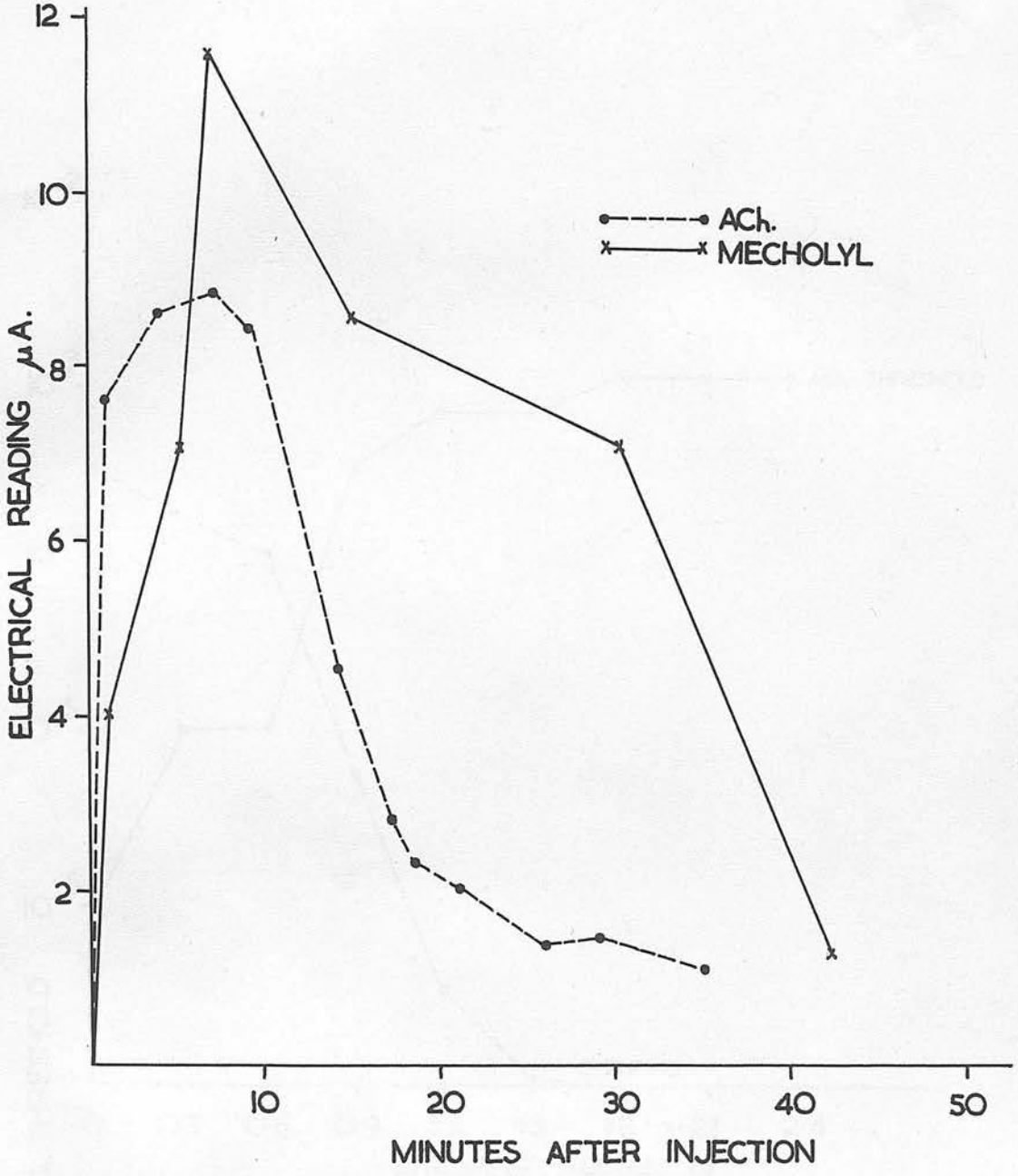
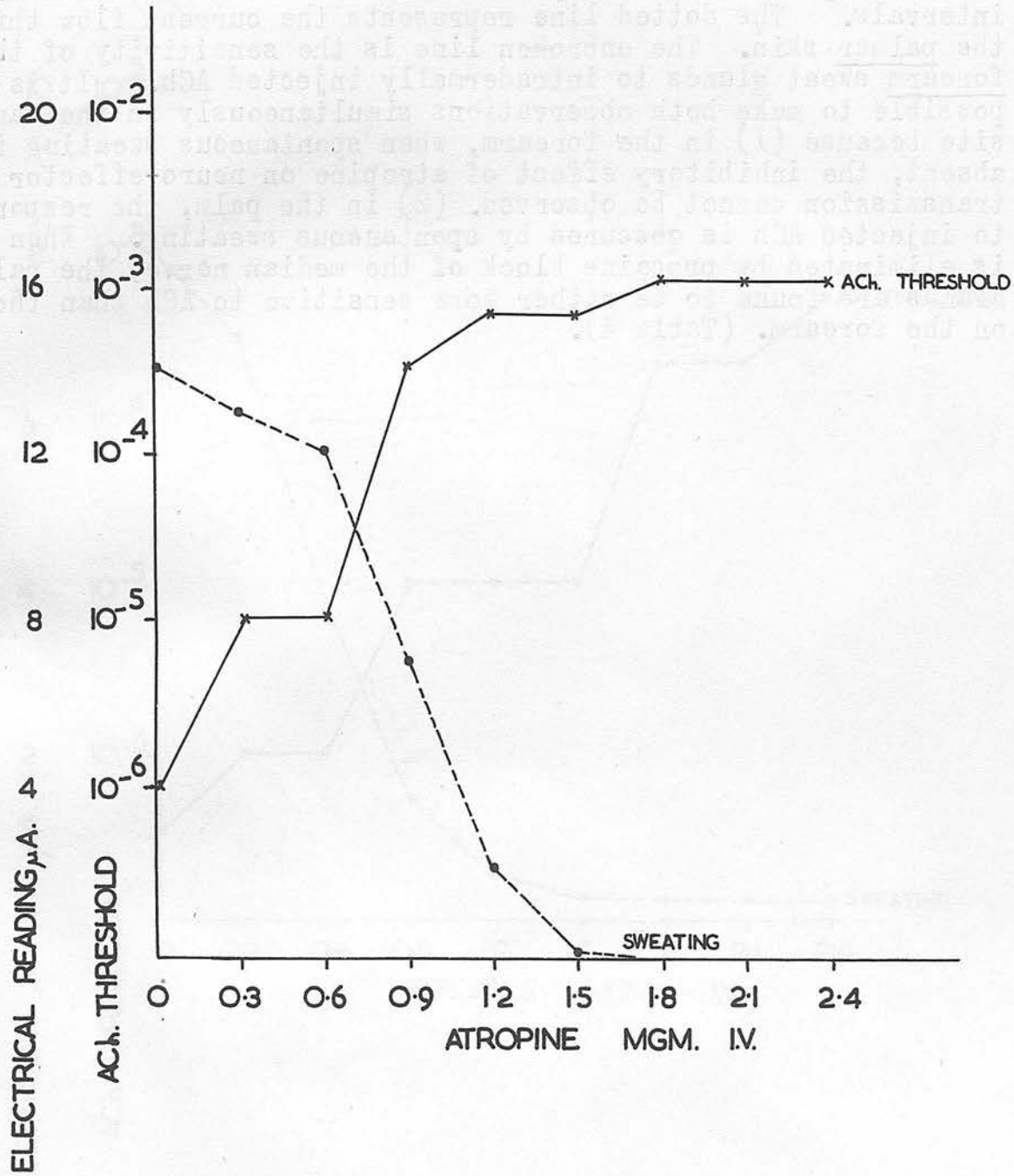


Fig. 2. Subject W.R. The drugs were injected intradermally at comparable sites in the same forearm. The electrical reading is the current flow through the skin at the site of injection.

Fig. 3. ATROPINE Vs. PALMAR SWEATING & ACh THRESHOLD.



P.T.O.

Fig.3. Subject H.J.R. In the experiments illustrated in figs.3 and 4 atropine was given by increments of 0.3mgm I.V at 5 min. intervals. The dotted line represents the current flow through the palmar skin. The unbroken line is the sensitivity of the forearm sweat glands to intradermally injected ACh. It is not possible to make both observations simultaneously in the same site because (1) in the forearm, when spontaneous sweating is absent, the inhibitory effect of atropine on neuro-effector transmission cannot be observed. (2) in the palm, the response to injected ACh is obscured by spontaneous sweating. When this is eliminated by procaine block of the median nerve, the palmar glands are found to be rather more sensitive to ACh than those on the forearm. (Table 4).

G.P.B. Fig. 4. ATROPINE Vs PALMAR SWEATING ACh THRESHOLD

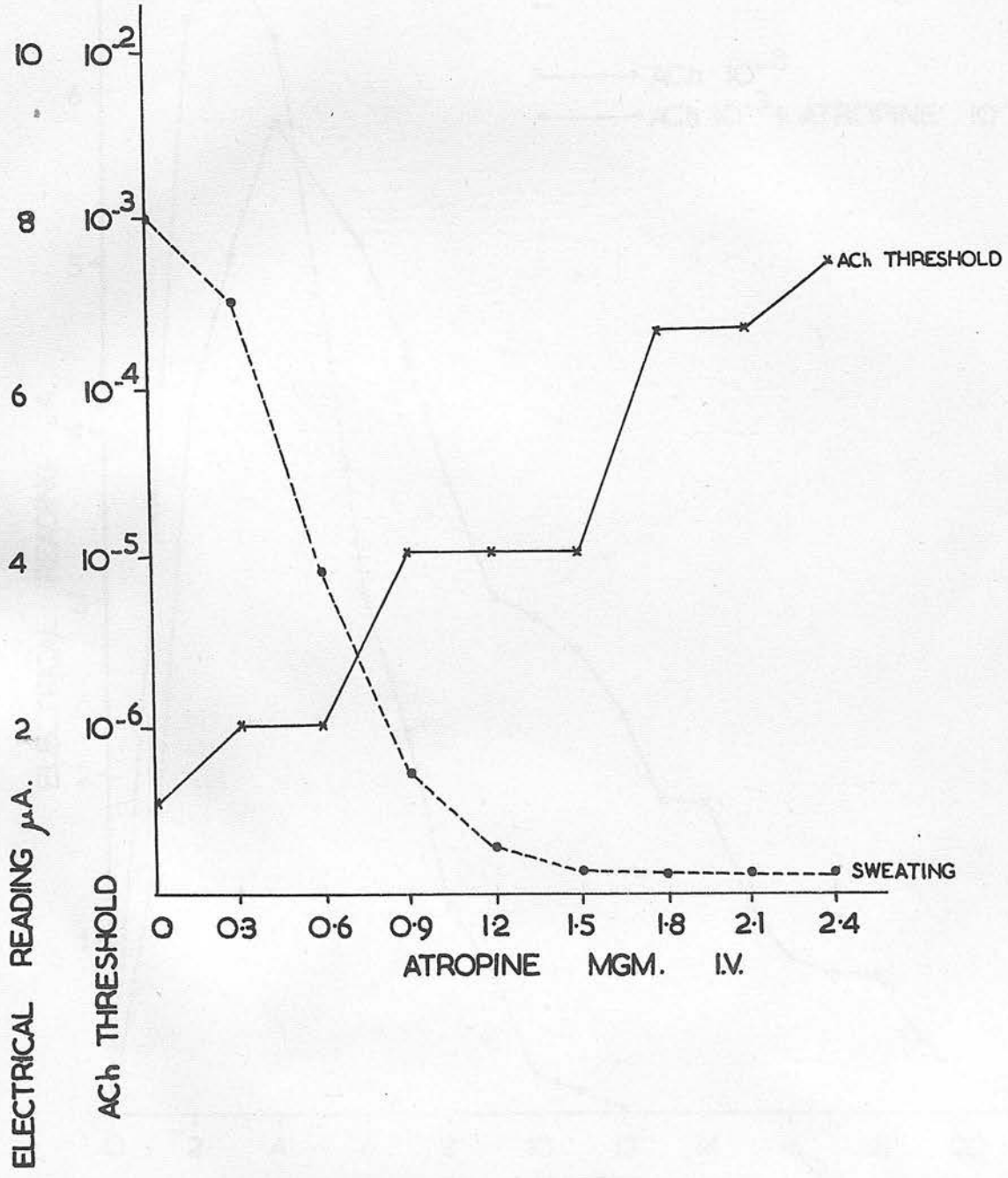


Fig.4. Subject G.P.B. See legend to Fig.3.

Fig. 5. TIME-COURSE OF SWEAT RESPONSE TO ACh AND ACh + ATROPINE.

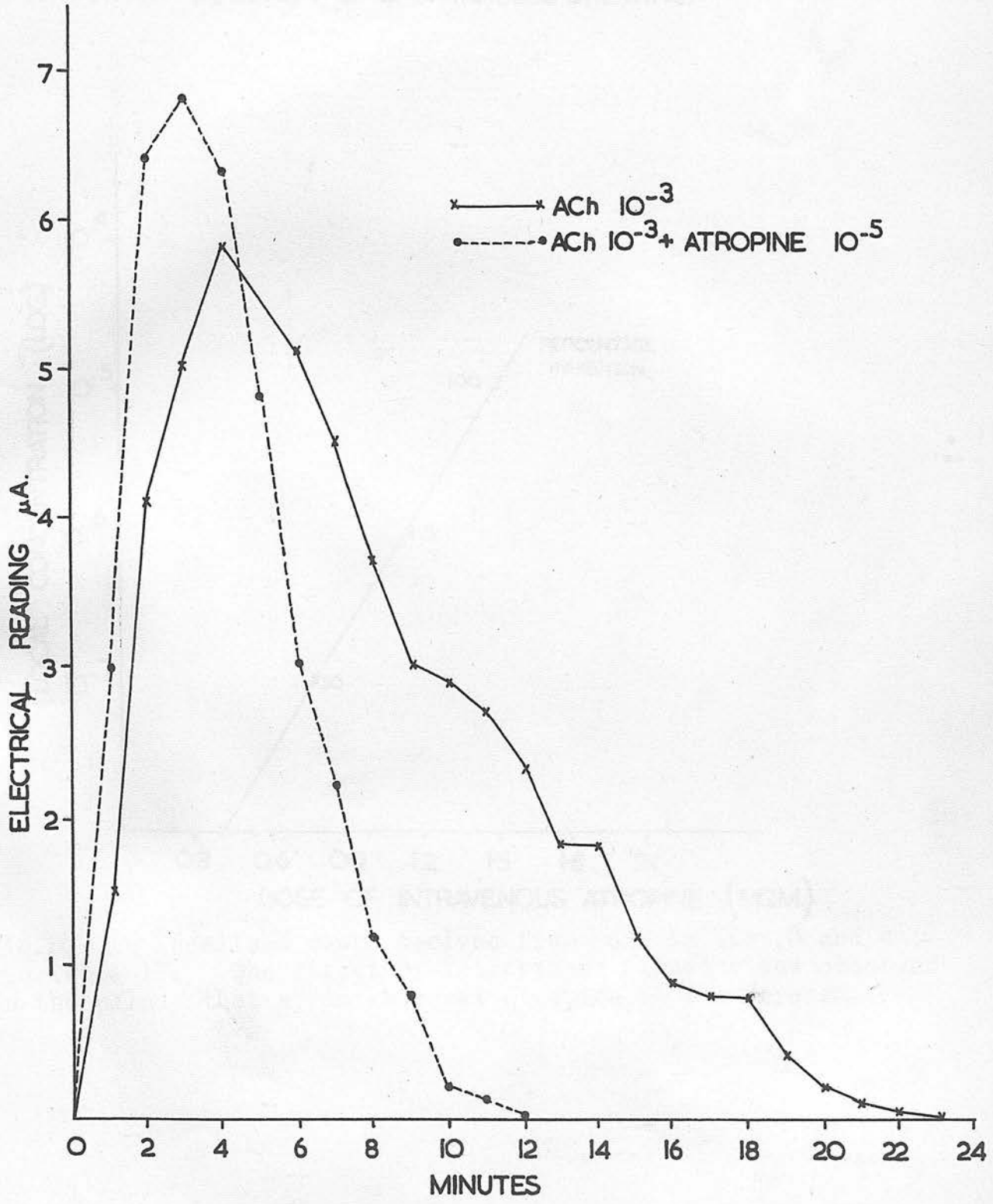


Fig. 5. Subject G. du B. The drugs were injected intradermally in the forearm.

g.6. INTRAVENOUS DOSE OF ATROPINE PLOTTED AGAINST LOCAL CONCENTRATION REQUIRED TO PRODUCE THE SAME PERCENTAGE INHIBITION OF SPONTANEOUS SWEATING.

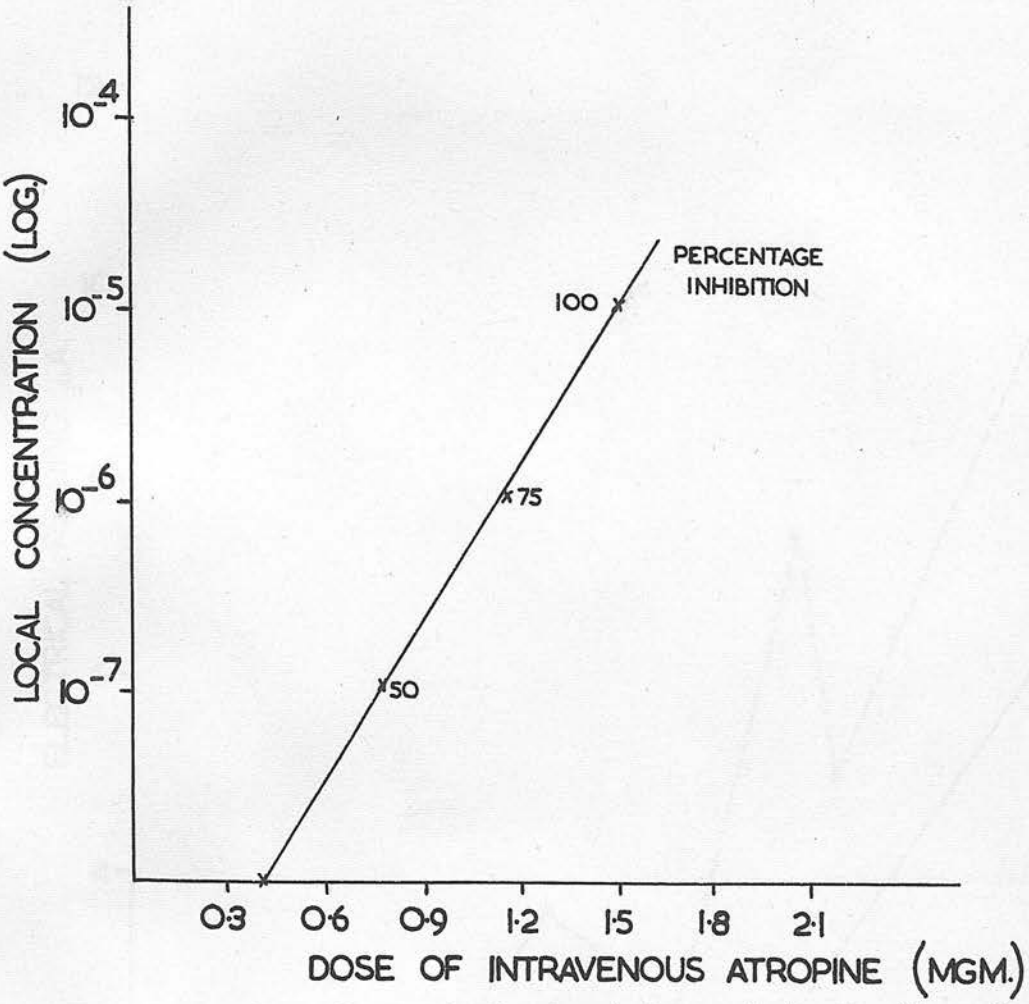
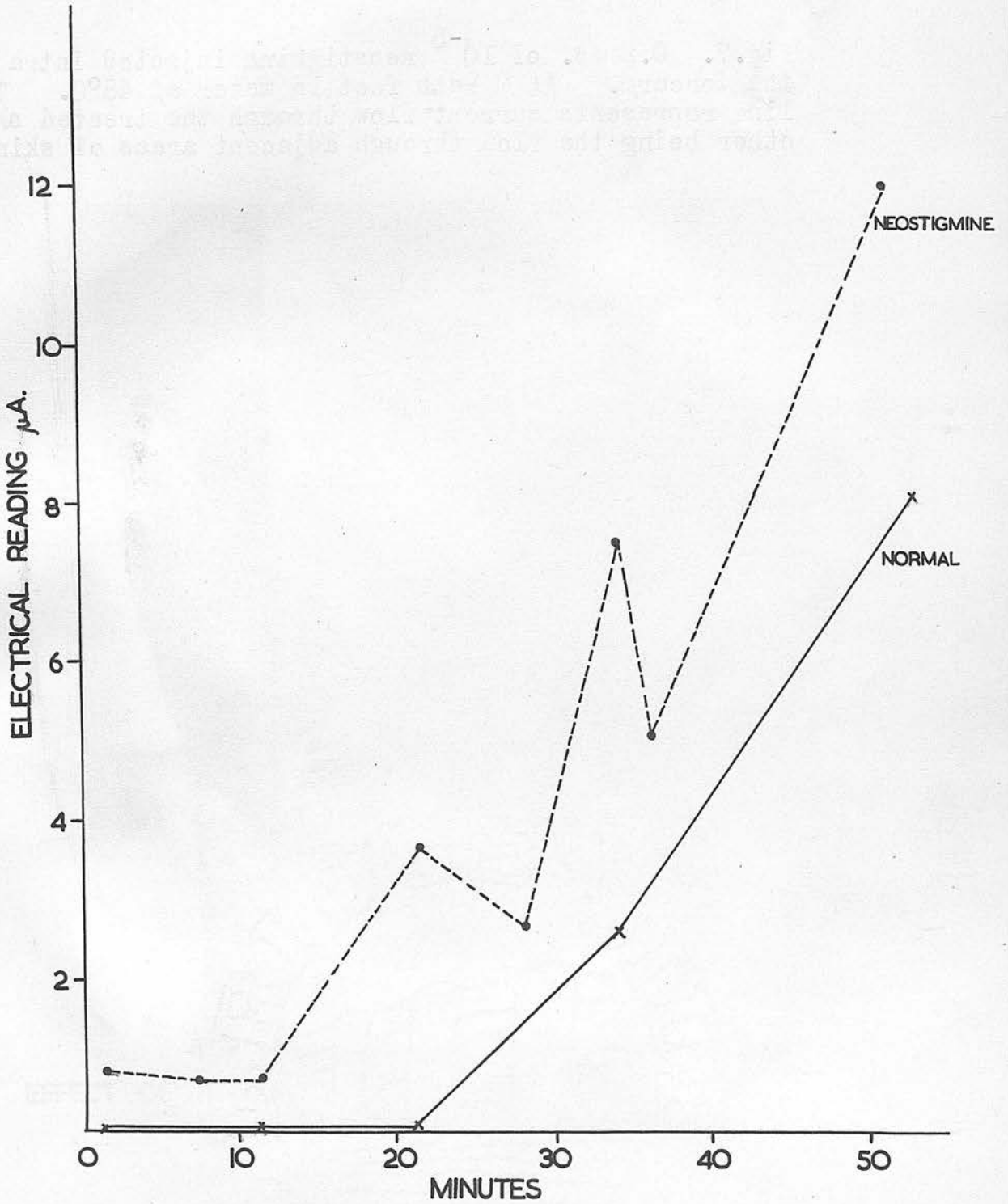


Fig.6. An idealised graph derived from data in figs.3 and 4 and Table 17. The effect of intravenous atropine was observed in the palm: that of intradermal atropine in the forearm.

Fig. 7 O.D. RELEASE OF ACh. BY SWEAT NERVE-ENDINGS DURING REFLEX HEATING REVEALED BY INTRADERMAL INJECTION OF NEOSTIGMINE.



P.T.O.

Fig.7. 0.2 cc. of 10^{-5} neostigmine injected intradermally in the forearm. At O both feet in water at 45°C. The broken line represents current flow through the treated skin, the other being the flow through adjacent areas of skin.

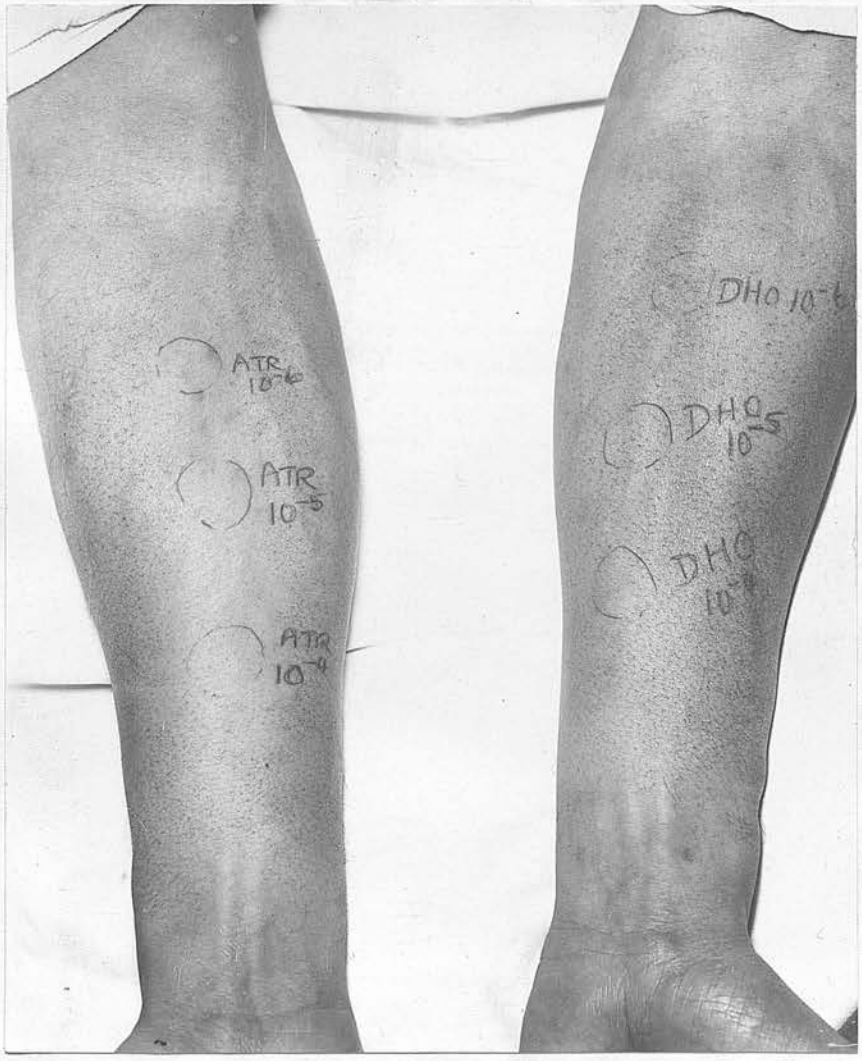
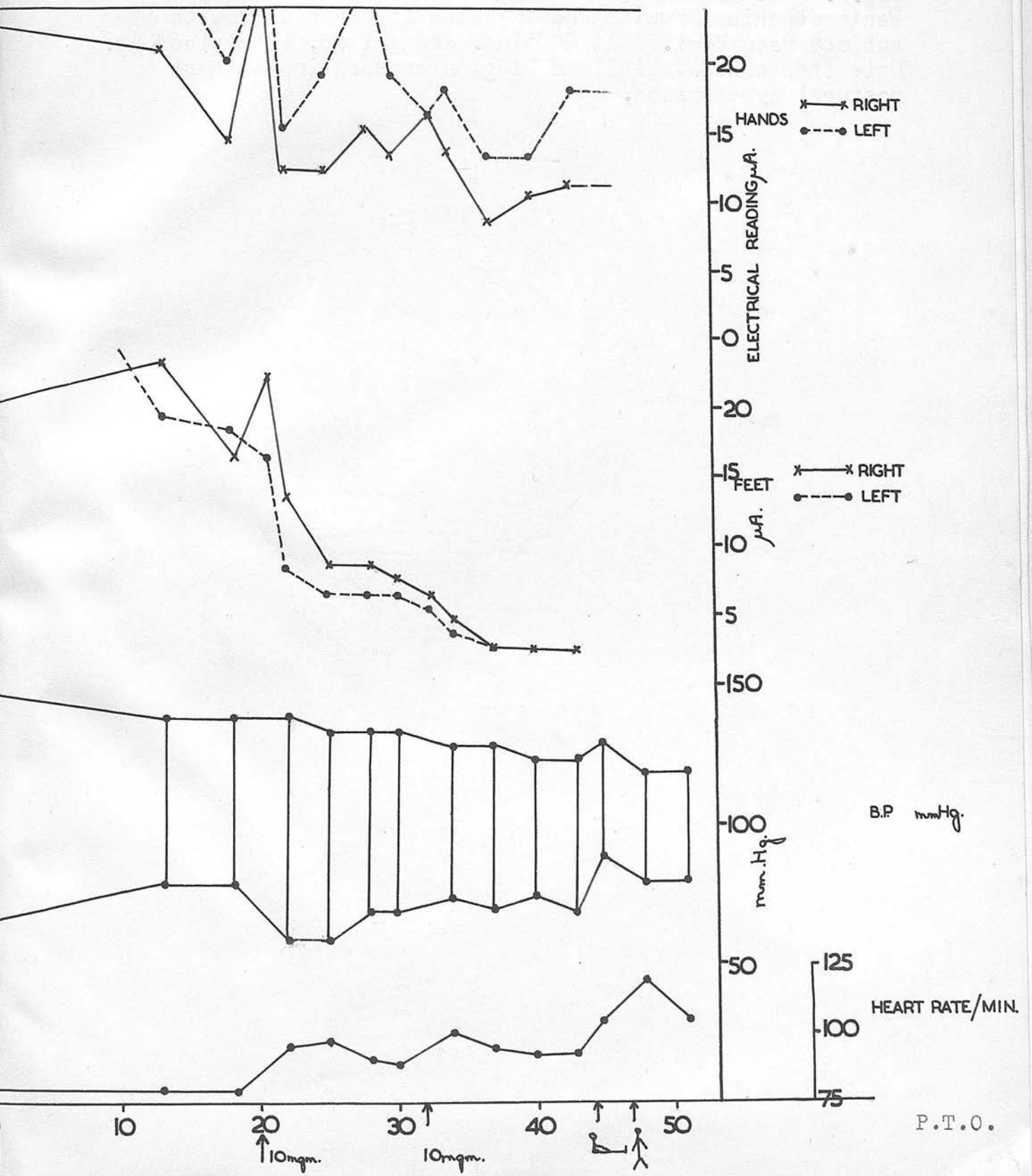


Fig.8. EFFECT OF INTRADERMAL ATROPINE AND DHO ON THE RESPONSE TO REFLEX HEATING.

P.T.O.

Fig.8. Subject G.S.P. Atropine (ATR) and dihydroergocornine (DHO) were injected intradermally (volume 0.2 cc), and sweating induced by heating the feet. The skin has been dusted with Quinizarin powder to show that sweating has been inhibited by atropine but not by DHO.

S.C. EFFECT OF PENTAMETHONIUM BROMIDE I.V. ON PALMAR, PLANTAR SWEATING AND ON B.P. AND PULSE RATE IN A CASE OF HYPERHIDROSIS.



P.T.O.

Fig.9. At 20 mins., and again at 32 mins., 10 mgm. of Pentamethonium Bromide was injected intravenously with the subject recumbent. At 44 mins. she sat up, then stood up. Note the marked inhibition of plantar sweating without postural hypotension.